UNIVERSITY OF UTAH
COLLEGE OF PHARMACY
L. S. SKAGGS PHARMACY INSTITUTE

UTAH MEDICAID DUR REPORT
MARCH 2017

NEW BASAL INSULINS

Insulin degludec
(Tresiba®)

Insulin glargine
(Lantus®, Toujeo®, Basaglar®)

Insulin detemir
(Levemir®)

Drug Regimen Review Center

Vicki Frydrych B.Pharm, PharmD, Clinical Pharmacist
Joanita Lake B.Pharm, MSc EBHC (Oxon), Clinical Pharmacist
Valerie Gonzales, PharmD, Clinical Pharmacist
JoanneLaFleur, PharmD, MSPH, Associate Professor

University of Utah College of Pharmacy

Contents

Introduction

In the United States, 29.1 million people (9.3% of the U.S. population) have diabetes.[1] In 2012, the estimated diabetes costs in the United States were $ 245 billion; direct medical costs were $ 176 billion, and indirect costs were $ 69 billion (disability, work loss, premature death).[1]

Patients with type 1 diabetes (T1DM) require insulin treatment due to a lack of insulin. Insulin options include rapid- acting, short-acting, intermediate-acting, long-acting, and premixed insulin.[2-4] In T1DM, insulin therapy regimens usually include a basal insulin with pre-meal, rapid-acting insulin injections.[5] Type 2 diabetes mellitus (T2DM) results from reduced insulin secretion or cellular insulin resistance.[6] Therefore, the mechanisms of action of the medications for type 2 diabetes include stimulating insulin release, decreasing absorption or hepatic production of glucose, and improving the insulin sensitivity of target organs.[7] Oral agents become less effective as beta cell function declines and it may be necessary to add an injectable medication such as insulin (or to switch to insulin) to manage blood glucose levels.[8] Estimates of the proportion of patients achieving a target HgbA1c (glycosolated hemoglobin) of <7% varies considerably for the different treatments, ranging from 26% with α-glucosidase inhibitors to 63% with the GLP-1 (glucagon-like peptide-1) agonist, exenatide. Basal insulins achieved target HgbA1c (A1C) in 39% of individuals and basal-bolus regimens achieved A1C target in 50% of individuals.[9,10]

A1C is a predictor of diabetes complications; higher A1C levels increase the likelihood of both microvascular and macrovascular complications (including renal, ophthalmic, neurologic and cardiovascular).[6,11] According to current guidelines, A1C target levels range from <6.5%[12,13] to <7%[3,14], although individualized goals may be higher (based on diabetes duration, age/life expectancy, comorbid conditions, known cerebrovascular disease or microvascular complications, risk of hypoglycemia, and other individual patient considerations).[15,16] Initially in T2DM, a trial of lifestyle modifications (such as medical nutrition therapy, weight loss, exercise and diabetes education) is recommended, but pharmacotherapy is often required due to persistent elevated glucose levels.[16] Insulin and sulfonylureas have been available since the early 1920's and the 1950's respectively[17,18], and until 1995, these were the only available drug classes for patients affected by type 2 diabetes.[19] Currently, 12 classes of medications are FDA-approved for treating type 2 diabetes, including biguanides (e.g. metformin), thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, glucagon-like peptide-1 (GLP-1) receptor agonists, amylin analogue, bromocriptine (dopamine agonist), alpha-glucosidase inhibitors, the bile acid sequestrant colesevelam, insulins, and the sodium-glucose co-transporter inhibitors (SGLT2).[19,20]

Insulin is indicated in the treatment of type 1 diabetes, type 2 diabetes, diabetes during pregnancy (preexisting and gestational), and in some patients without diabetes (e.g. glucose control in critical care or sepsis treatment).[21] Insulin functions to suppress hepatic glucose production, lipolysis, proteolysis, gluconeogenesis and promote glycogen synthesis and transport of glucose into adipocytes and myocytes.[22] Basal insulin secretion accounts for 40% of the body's daily insulin secretion. Basal insulin secretion inhibits hepatic glycogenolysis, ketogenesis and glconeogenesis.[23,24].

Early integration of insulin into the treatment of T2DM may preserve β-cell function, improve insulin sensitivity and slow disease progression.[25] Insulin is available as recombinant human insulin

(regular and NPH) and modified insulin analogs with rapid onset (e.g. insulin lispro, insulin aspart, insulin glulisine), short-acting (insulin regular), intermediate-action (NPH), long-acting/extended duration (e.g. insulin glargine, insulin detemir, insulin degludec) or in combination (e.g. insulin degludec + insulin [7/30], NPH + regular insulin [70/30, 50/50], insulin lispro protamine + insulin lispro [75/25, 50/50], and insulin aspart protamine + insulin aspart [70/30]).[26,27] All long-acting, basal insulins are available in prefilled disposable pens.[28-32] Levemir and Lantus are additionally available in 10 mL vials.[30,32]

Insulin is usually administered subcutaneously (90-degree angle to skin) in the abdomen, outer thigh, back of arm, or flank/buttocks.[21] Insulin may be administered with disposable plastic syringes (1.0, 0.5, and 0.3 mL sizes) or via insulin pens. Injection sites should be rotated to avoid lipohypertropy and the needle should be left in place for 5-10 seconds after injecting to avoid leaking.[21] Insulin injections in the abdominal wall are absorbed most rapidly and may be preferred for pre-meal injections while absorption from the leg or buttock occurs more slowly and may be appropriate with evening administration of intermediate-acting insulin.[5] Glycemic control is affected by many factors including the type of insulin (onset, peak, activity, duration), preparation, the size of the subcutaneous depot, injection site and subcutaneous blood flow.[8] Inter- and intra-patient absorption variability of 25-50% is reported for all insulin preparations, especially for longer acting insulins.[5] The safe and effective use of insulin requires patients or caregivers to have visual acuity, adequate motor skills for use of insulin syringes or pens, and cognitive ability.[33,34]

Dose-taking compliance statistically differed when patients with diabetes were assigned ≥3 doses of any therapy per day. [35] Using the Morisky-Green questionnaire (self-administered), the best compliance (67%) was found in patients receiving insulin monotherapy and lowest in patients receiving combination insulin and oral antihyperglycemic medications (39%).[36] Nonadherence to any initial diabetes regimen increased the rate of hospitalization and Emergency Department (ED) visits by 13% compared with adherent patients.[37] Conversely, patients who were initially adherent and become nonadherent demonstrated a 15% increased rate of hospital and ED utilization versus adherent patients.[37] Adherence improves when patient's emotional well being is considered and they understand the treatment regimen and benefit (especially for complex regimens), adverse effects and medication costs.[38] Strategies associated with improved adherence include lessening regimen complexity to reduce the risk of hypoglycemia and adverse reactions.[38] Patient compliance remains an unresolved issue for insulin administered via subcutaneous injection, thus several other delivery systems have been under investigation including buccal, oral, rectal, ocular, nasal, and transdermal routes.[39,40]

- Utah Medicaid instituted a Prior Authorization (PA) for use of insulin pens on 3/1/13 which was rescinded in December 2016. The criteria had included,
    - legal blindness
    - debilitating rheumatoid or osteoarthritis of one or both arms, hands, and/or one or more fingers
    - other conditions causing severe debilitation of one or both arms, hands, and/or one or more fingers
    - reductive deformities of one or both arms, hands, and/or one or more fingers
    - Parkinsonism or essential tremor
    - mental retardation (severe intellectual disability)

- any condition that necessitates that a patient, greater-than-or-equal-to the age of 19 years, have a legal guardian other than him/herself"
- "*Note: patient age of less-than-or-equal-to the age of 18 years is not sufficient justification for approval of insulin pens(s)".*[41]

The purpose of this review is to ensure appropriate use of long-acting basal insulins (insulin detemir, insulin glargine and insulin degludec). Basal insulin analogues provide peak-less basal insulin coverage with sustained glucose lowering, a low risk of hypoglycemia, possibility of alternate dosing schedules and safety in combination with oral hypoglycemic agents. The more concentrated insulin preparations reduce the volume of each injection, limit the number of injections required per dose/day, reduce pain, discomfort, leakage, unpredictable absorption, and may improve adherence and patient satisfaction.[42] The availability in pen injectors improves delivery and reduces errors associated with syringe and needle administration.[42]

Insulin options

Appendix 1 contains a product comparison table for the basal insulin analogues degludec, detemir, glargine and the traditional basal insulin, neutral protamine Hagedorn (NPH) insulin.[2,3] Appendix 2 contains a pharmacokinetic comparison of the basal insulins. None of the basal analogues are available in generic formulation. Basaglar is a "biosimilar" or "follow-on" insulin of identical amino-acid sequence as insulin glargine.[43] According to the FDA, "A biosimilar product is a biological product that is approved based on a showing that it is highly similar to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products."[44] Basaglar was found non-inferior to insulin glargine in A1C lowering in both T1DM and T2DM with no difference in dose, mean blood glucose or hypoglycemia.[45,46]

Methodology

A Cochrane Library literature search for systematic reviews was conducted. Medline (PubMed), Embase, UptoDate, the Agency for Healthcare Research and Quality (AHRQ), American Diabetes Association (ADA) website, the FDA website (including product labeled information), Micromedex and Lexicomp were searched for safety information, systematic reviews, clinical trials, and guidelines. As per the hierarchy of evidence, high quality systematic reviews and evidence-based guidelines were searched for first.

Clinical Practice Guidelines

Clinical practice guidelines for treatment of diabetes are available from the American Diabetes Association[47], Canadian Diabetes Association[48,49], European Association for the Study of Diabetes[50], American Association of Clinical Endocrinologists & American College of Endocrinology[51], and National Institute for Health and Care Excellence[52,53]. Patient populations addressed include T1DM, T2DM, pregnancy, children and adolescents, the elderly and hospitals. Safety guidelines and recommendations are available from the Centers for Disease Control and Prevention[54,55], Institute for Safe Medication Practices[56,57] and National Institute for Health and Care Excellence.[58] Clinical practice guidelines for use of long-acting, basal insulin products are presented in Table 1.

All guidelines recommend individualization of the target A1C goal.[47,48,51,59] The American Diabetes Association suggests an A1C goal in non-pregnant adults of <7% with a more stringent goal of <6.5% in highly motivated individuals if it may be achieved without significant hypoglycemia (e.g shorter duration of diabetes, T2DM treated with lifestyle or metformin only, long life expectancy or no significant cardiovascular disease). A less stringent goal of <8% may be appropriate in individuals with a history of severe hypoglycemia, advanced macro- or micro-vascular complications, extensive comorbidities, long-standing diabetes and inability to achieve lower threshold targets.[14] The Canadian breakpoints for similar patient groups are ≤7%, ≤6.5%, 7.1-8.5%.[60] The American Association of Clinical Endocrinologists and American College of Endocrinology suggest two A1C breakpoints.[51] A target A1C goal of ≤6.5% is recommended if it can be achieved without significant hypoglycemia or other complications. A target of >6.5-8% is recommended for those in whom the lower threshold cannot be achieved without adverse outcomes. ADA guidelines for glycemic control in the elderly define three A1C breakpoints at <7.5% for the healthy-aged, <8% for the complex/intermediately ill-aged and <8.5% for the very complex aged in poor health.[61]

T1DM insulin therapy includes subcutaneous insulin infusion administration (SIIA) or basal-bolus therapy. The choice of therapy involves consideration of treatment goals, age, duration of diabetes, lifestyle, diet, general health, motivation, hypoglycemia awareness status, self-management ability, socioeconomic status, financial factors and patient-, family- and provider-preferences. Basal therapy with long-acting analogues (vs NPH) may result in lower fasting plasma glucose levels and less nocturnal hypoglycemia.

In T2DM, insulin therapy is recommended initially if the A1C or blood glucose is high (guidelines differ on the threshold), if the patient has symptomatic hyperglycemia, metabolic decompensation or if diabetes is long-standing. In these instances, initiation of dual therapy may be considered. For other patients, the choice of therapy should consider the degree of hyperglycemia, cardiovascular and end-organ complications, age, patient preference, motivation, access to treatments, effectiveness, risk of hypoglycemia, effects on weight, side effects, contraindications and cost. Lifestyle management is at the core of all diabetes therapy. Metformin remains the preferred initial agent for type 2 diabetes if tolerated and not contraindicated (e.g. glomerular filtration rate above 45 mL/min or significant heart failure). If glycemic goals are not achieved in 3 months with maximally tolerated metformin or alternative non-insulin medication, therapy should advance. A second oral agent (e.g. sulfonylurea, thiazolidinedione (TZD), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonist, sodium-glucose co-transporter 2 (SGLT2) inhibitor or insulin should be added. If the target goal remains unmet, triple therapy is recommended. Most patients will require insulin therapy eventually. Basal analogues (detemir or glargine) compared with NPH may reduce the risk of nocturnal and symptomatic hypoglycemia. The addition of insulin therapy to oral therapy is preferred with a single daily dose of basal insulin. The ADA recommendations state, "people with type 2 diabetes without a history of hypoglycemia may use NPH insulin safely and at a much lower cost."[47] The National Institute for Health and Care Excellence also prefer initial insulin therapy with NPH once or twice daily. The American Association of Clinical Enocrinologist and American College of Endocrinology *prefer basal insulins* over NPH even though achieved glycemic control is similar. The advantages of basal therapy include long duration of action, flat serum insulin concentrations with minimal/no peak, less hypoglycemia and the availability of concentrated formulations. Varieties of medications are added to basal therapy if glycemic goals are not reached. When basal-oral therapy has not met glycemic goals,

consider the addition of a single dose of rapid acting insulin before the largest meal of the day. Overall, basal-bolus therapy is the most effective insulin regimen.

Insulin is the drug of choice for treating preexisting and gestational diabetes in pregnancy. A regimen using multiple daily injections is preferred. Insulin doses vary by trimester, high doses and concentrated insulins may be required and a high risk of post-delivery hypoglycemia occurs with a return to normal insulin sensitivity within 2-3 weeks. Alternatives include metformin and glyburide which cross the placenta and lack long-term safety data. Guidelines suggest that basal insulins, detemir and glargine, may be used in place of NPH. Levemir may be the safest choice with FDA pregnancy category designation “B”, while Basaglar, Lantus and Tresiba are assigned category “C”. Toujeo includes the new FDA narrative subsections that state fetal risk cannot be ruled out.

Children and adolescents with T1DM and T2DM are treated to the same glycemic targets. Multidisciplinary care is essential. High blood glucose, A1C or undifferentiated T1DM vs T2DM should receive insulin therapy initially. T1DM may be associated with a 2 year honeymoon period. In T1DM, basal-bolus or SIIA are equally preferred. Children with T2DM presenting with high A1C (≥9%) or severe metabolic decompensation should receive insulin therapy initially. If the A1C is above 7%, pharmacotherapy with metformin is recommended. In other youth, if lifestyle therapy fails after 3-6 months, monotherapy with metformin, glimepiride or insulin should be initiated.

In the elderly, glycemic targets are individualized. Reducing the risk of hypoglycemia is more important than glycemic control. Minimizing the number of daily insulin injections is preferred. The use of premixed insulins and prefilled insulin pens may reduce dosing errors. Glycemic control is similar with basal-bolus and premixed insulin therapy. Insulin therapy requires cognitive ability, and good visual and motor skills. Basal insulins (detemir and glargine) are associated with less hypoglycemia and dosing errors than NPH or premixed insulin and may be a good option in the elderly. Poorly controlled therapy may include SIIA.

In the hospital setting, use of insulin, hypoglycemia and self-managment pathways are recommended. In critically ill patients SIIA may be preferred, while basal-bolus insulin therapy is recommended in non-critically ill patients. Sole use of sliding scale insulin is strongly discouraged.

Guidelines concerning insulin safety state that insulin pens should not be shared due to the risk of blood-borne pathogen transmission. Insulin should never be withdrawn from an insulin pen (especially with concentrated insulins). The word “units” should always be spelled out, and only insulin syringes marked in mL should be used. Hospitalized individuals should be able to self-administer insulin (via protocol) to reduce the harm of incorrect timing with respect to food.

Currently, practice guidelines do not clearly address concentrated insulin use in the setting of intercurrent illness, hemodynamic instability, diet, stress, concurrent medications (e.g. glucocorticoids) or during hospitalization.

Table 1: Guidelines for Use of Long-acting Basal Insulins in the Treatment of Diabetes Mellitus (See guidelines for full recommendations concerning use of other therapies, including non-basal insulins)

Source	Recommendations

Pharmacologic Approaches to Glycemic Treatment[62] (American Diabetes Association, 2017)	Type 1 DM
	• Insulin is the mainstay therapy, starting with 0.4-1 units/kg/day
	  ○ Multiple daily injections of basal and bolus insulin OR subcutaneous insulin infusion
	  ○ Insulin requirements are higher during puberty
	  ○ Rapid acting insulins reduce the hypoglycemia risk
	  ○ Balance intensive therapy with hypoglycemia risk
	
	Type 2 DM
	• Consider insulin for newly diagnosed, symptomatic, A1c ≥10% or blood glucose ≥300 mg/dL
	• Consider Dual Therapy (which may include insulin) if A1C is ≥9%
	  ○ Insulin may be effective when other agents are not, is effective vs severe hyperglycemia and should be considered in the presence of weight loss, ketosis, polyuria, polydipsia
	• Consider adding insulin to maximally tolerated noninsulin therapy at 3 months (one of a number of possible options)
	  ○ Choice of agent depends on efficacy, hypoglycemia risk, impact on weight, potential side effects, cost, patient preference
	  ○ Empaglifozin/liraglutide may be used or added to insulin especially with long-standing poorly controlled T2DM and established atherosclerotic cardiovascular disease
	• Do not delay insulin therapy if glycemic goals are not being met
	• Most patients will eventually require insulin therapy
	
	Initial Basal Insulin Therapy
	• **"People with type 2 diabetes without a history of hypoglycemia may use NPH insulin safely and at much lower cost"**
	• Begins with basal therapy, 10 units/day or 0.1-0.2 units/kg/day
	• Adjust twice weekly to target by 10-15% or 2-4 units
	  ○ Hypoglycemia without reason, decrease dose 4 units or 10-20% per day
	
	Dual Insulin Therapy
	If not at goal A1C, consider combination
	  ○ With rapid acting insulin before largest meal OR
	  ○ Addition of GLP-1 RA OR
	  ○ Change to premixed insulin twice daily
	
	General
	• Patients should have an algorithm for self-titration, self-monitoring
	• In patients requiring high-dose basal therapy consider concentrated basal insulin; U300 glargine and U200 degludec

Pharmacologic Management of Type 2 Diabetes: 2016 Interim Update (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2016)[59]	• Presentations of symptomatic hyperglycemia and metabolic decompensation should receive an initial regimen containing insulin ± metformin • A1C <8.5% and goals not achieved with 2-3 months medication and lifestyle management, consider combination therapy with insulin an option. • Choice of additional pharmacological treatment should consider the degree of hyperglycemia, risk of hypoglycemia, overweight or obesity, cardiovascular disease or multiple risk factors, comorbidities (renal, congestive heart failure, hepatic, etc), patient preferences and access to treatment. ○ In the presence of clinical cardiovascular(CV) disease choose a antihyperglycemic with demonstrated CV outcome benefit • **When basal insulin is added to a antihyperglycemic regimen, long-acting analogues (detemir or glargine) may be used instead of NPH to reduce the risk for nocturnal or symptomatic hypoglycemia.** • Counseling should be offered for individuals using or starting insulin about the prevention, recognition and treatment of drug-induced hypoglycemia.

Management of Diabetes in Pregnancy[63] (American Diabetes Association, 2017)	General
	• In pregnancy the A1C goal is lower due to increased red blood cell turnover (<6% to <7% dependent upon hypoglycemia risk).
	• Lower rates of adverse fetal outcomes with A1C < 6-6.5%
	
	Preexisting Diabetes (Type 1 or Type 2)
	• Insulin is the preferred agent. Titrate dosage with frequent self-monitoring of blood glucose
	  ○ T2DM insulin doses may be quite high, necessitating concentrated insulins
	• 1st trimester often require less insulin (especially in T1DM with increased risk of hypoglycemia)
	• 2nd trimester increasing glucose resistance (weekly/biweekly adjustments to glycemic target)
	  ○ Overall, smaller basal doses and larger bolus/prandial doses
	• Late 3rd trimester reduced insulin requirements possible
	• Following delivery insulin sensitivity increases (returns to normal over 1-2 weeks)
	
	Preexisting Type 2 Diabetes
	• Insulin is preferred medications (metformin and glyburide may be used but cross the placenta and lack long term safety data)
	  ○ Following delivery insulin sensitivity increases (returns to normal over 1-2 weeks)

Source	Recommendations
	Gestational Diabetes (If diet and exercise are inadequate) • Insulin is preferred medications (metformin and glyburide may be used but cross the placenta and lack long term safety data)
Diabetes and Pregnancy (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2013)[64]	Preexistent T1DM or T2DM • Individualized insulin regimen and glycemic targets using intensive insulin therapy (FPG <95 mg/dL; 1-hour prandial <140 mg/dL; 2-hour prandial <120 mg/dL) o Individualize based on severe hypoglycemic risk o Basal insulin may use detemir or glargine instead of NPH • Monitor post-partum for high risk of hypoglycemia Gestational Diabetes • Glycemic targets same as above • Initiate insulin if 2-weeks of nutritional therapy do not achieve glycemic targets • Insulin therapy is preferred with multiple daily injections o Similar outcomes with short-acting analogues vs regular insulin • Patients who refuse or are nonadherent to insulin may receive off-label metformin or glyburide
Older Adults[61] (American Diabetes Association, 2017)	• Hypoglycemia and hyperglycemia should be avoided, individually adjust glycemic targets o Hypoglycemia increases the risk of cognitive defects and cognitive defects increase the risk of hypoglycemia • Insulin therapy requires good visual skills, motor skills and cognitive ability (or an able caregiver) • Glycemic targets should be individualized (e.g. HgbA1c <7% to <8.5%) • Attempt to minimize the number of daily insulin doses o Once-daily basal injection may be a reasonable option in many older patients
Diabetes in the Elderly (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2013)[64]	Individualized therapy to promote patient safety • Medication dose errors and glycemic control may be minimized with premixed insulins vs mixing insulins and prefilled insulin pens vs conventional syringes o Premixed advantage: can be injected after a meal, may give better glycemic control than basal insulin o Premixed disadvantage: increased risk of hypoglycemia and greater weight gain • Glycemic control similar with basal-bolus vs premixed insulin o Basal-bolus regimens may be associated with greater improvements with overall glycemic control, health status and mood than twice-daily injections of long-acting insulin. • Poorly controlled T2DM requiring insulin may be managed with CSII or basal-bolus regimens • **Detemir and glargine are associated with lower rates of hypoglycemia than NPH or 30/70 insulin**
Children and Adolescents[65] (American Diabetes Association, 2017)	• A1c goal of <7.5% across all age-groups • Treatment goals identical for T1DM and T2DM in youth • Multidisciplinary care is essential • Youth with blood glucose ≥250 mg/dL of A1c >9% or undifferentiated T1 vs T2DM should receive insulin • T2DM treatment includes insulin and/or metformin
Type 1 diabetes in children and adolescents (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2013)[64]	Insulin remains the mainstay therapy • Choice of insulin regimen depends on child's age, duration of diabetes, family lifestyle, socioeconomic factors, and family, patient and physician preferences • Honeymoon period of up to 2 years associated with low (<0.5 units/kg/day) insulin requirement • Basal-bolus or continuous subcutaneous insulin infusion administration (CSII) o CSII may give slightly improved metabolic control o Conflicting information whether basal therapy with glargine or detemir reduces A1C o Neither regimen is preferred to minimize non-severe hypoglycemia
Type 2 diabetes in children and adolescents (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2013)[64]	Target A1C ≤7.0% Children with T2DM and A1C ≥9.0% or those with severe metabolic decompensation (e.g. DKA) • Initiate insulin therapy • May be weaned off once glycemic target achieved If glycemic targets are not achieved within 3-6 months by lifestyle modification, consider monotherapy o Metformin o Glimepiride (metformin preferred over glimepiride) o Insulin Presentation with A1C >7% • Consider therapy upon presentation with metformin
Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the	Decision to start insulin therapy should consider patient's motivation, cardiovascular and end-organ complications, age, general well-being, risk of hypoglycemia, and overall health status as well as cost considerations. • Consider insulin if A1C is >8% and/or longstanding type 2 diabetes (less likely to achieve goal with a third oral agent). o Although GLP-1 RA may lower glycemia, insulin will likely be required • **Initiate insulin therapy with a single daily dose of basal insulin ADDED to the regimen.** o Adjust to target glycemic goal while avoiding hypoglycemia.

Source	Recommendations
comprehensive Type 2 Diabetes Management Algorithm – 2017 Executive Summary[51]	○ Titration can be managed by the provider or the patient ○ **Basal insulin analogues are PREFERRED OVER NPH even though no differences in achieving glycemic control** ▪ Provide a flat serum insulin concentration for up to 24 hours ▪ Less hypoglycemia than NPH ▪ Concentrated and longer-acting basal analogues (glargine U300, degludec U100 and U200) yield prolonged and stable PK/PD vs glargine U100 or detemir. • Glycemic control is equivalent with reduced rates of severe or confirmed hypoglycemia (especially nocturnal) vs glargine or detemir U100 (evidence is lacking for degludec vs glargine U300) ▪ Hypoglycemia is more common with premixed insulins than basal-bolus regimens, although simpler regimens may be preferred in some patients. • Patients not achieving glycemic goal on basal insulin ○ Consider the addition of GLP-1 RA, SGLT-2 inhibitor, DPP-4 inhibitor ▪ The dosage of basal insulin may require a reduction • Patients not achieving glycemic control on basal ± oral therapy ○ Consider the addition of mealtime insulin to cover postprandial hyperglycemia or when the total daily basal dose exceeds 0.5 units/kg (beyond this hypoglycemia risk is increased without significant A1c reduction • **Basal-bolus regimens are the most effective insulin regimen, providing flexibility for mealtimes and meal CHO content (con: weight gain).**
Pharmacotherapy in T1DM (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Interim Update, 2015)[49]	• Basal-bolus or SCII are the regimens of choice for all adults with T1DM ○ Individualize regimens to treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status, self-management ability, and social and financial issues. • Basal-bolus using rapid-acting insulin analogues may result in improved postprandial glycemic control and A1c with minimized hypoglycemia • **Basal-bolus using long-acting analogues detemir or glargine results in lower fasting plasma glucose levels and less nocturnal hypoglycemia compared with once- or twice-daily NPH insulin** <u>Twice daily bolus dosing</u> ○ Glargine is longer acting than detemir, yet 15-30% of patients using insulin glargine will experience pre-injection hyperglycemia requiring twice-daily administration. ○ **Twice daily detemir vs NPH in basal-bolus regimens resulted in less nocturnal hypoglycemia**
NICE: Type 1 diabetes in adults: diagnosis and management [NG17][52]	• Insulin therapy ○ Regimen of choice for all adults: Multiple daily basal-bolus injection regimens are preferred over twice-daily mixed insulin regimens ○ Do not offer any newly diagnosed person a non-basal-bolus regimen Long-acting insulin • **Offer twice-daily insulin detemir as basal insulin therapy** • Alternative ○ an existing insulin regimen achieving agreed targets ○ **once daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person or once-daily insulin detemir is not tolerated** ○ Consider other basal insulin regimens if targets are not achieved with consideration of patient preferences and acquisition cost
Pharmacologic Management of T2DM (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Interim Update, 2015)[49]	• Lifestyle management for 2-3 months is preferred unless the A1C is ≥8.5% (initiate therapy with 2 agents) or the patient has symptomatic hyperglycemia and metabolic decompensation (initiate insulin therapy) Pharmacologic therapy choices should consider degree of hyperglycemia, comorbidities, patient preference, access to treatments, effectiveness and durability of the agent, risk of hypoglycemia, effectiveness to reduce diabetic complications, effects on body weight, side effects and contraindications • Metformin should be the initial medication used for overweight patients • Combinations of medications should be used to attain target A1C within 3-6 months • **The addition of basal therapy (detemir or glargine) may be preferred to NPH to reduce the risk of nocturnal and symptomatic hypoglycemia** • The addition of bolus therapy may be preferred with rapid-acting analogues vs regular insulin to improve glycemic control and reduce the risk of hypoglycemia
Type 2 diabetes in adults: management [NG28][53]	• Reinforce diet, lifestyle and drug therapy adherence • Individualize HbgA1c target goal • Choose drug therapy based on effectiveness, safety, tolerability, individual clinical circumstances, prefernces and needs, available agents, costs • Symptomatic hyperglycemia consider insulin or sulfonylurea • In metformin-tolerant individuals metformin ± other therapies (not insulin) for intensification ○ insulin is not considered as an option (vs triple therapy) until HbgA1c reaches 7.5% • When metformin is contraindicated or not tolerated other therapies are initiated and intensified ○ Insulin is an option at HgbA1c threshold of 7.5% Insulin-based treatment

Source	Recommendations

	• Structured program, continue metformin in tolerant individuals
	• **Initial therapy: NPH once or twice daily**
	  ○ Consider NPH and short-acting insulin separately or as a pre-mixed (especially with HgbA1c ≥9.0%)
	  ○ Consider alternative to NPH, insulin detemir or glargine (or biosimilar), IF
	  ▪ Needs assistance to inject insulin
	  ▪ Lifestyle is restricted by recurrent symptomatic hypoglycemia
	  ▪ Requires twice-daily NPH in combination with oral hypoglycemic medications

Consensus on Insulin Dose and Titration Algorithms in Ambulatory Care of Type 2 Diabetes in India[66]	• **Start basal insulin (degludec/glargine/detemir**) as 10 units once daily at bedtime • Titrate to FPG of 80-130 mg/dL • Adjust once weekly based on lowest/mean value of 3 most recent FPG values • Reduce the dose 10-20% with hypoglycemia (<70 mg/dL)
Diabetes Care in the Hospital (American Diabetes Association, 2017)	• Sole use of sliding scale insulin is strongly discouraged • All institutions should have a hypoglycemia management protocol including medical record documentation • When blood glucose is <70 mg/dL the treatment regimen should be reviewed and changed as necessary • Use structured discharge plans for individual patients with diabetes <u>Critically Ill Patients</u> • Insulin therapy is started with persistent hyperglycemia (≥180 mg/dL) • Target glucose range is 140-180 mg/dL (also for non-critically ill) • Individualized goal of < 140 mg/dL if significant hypoglycemia can be avoided • Insulin infusions (intravenous) used according to validated protocols with infusion rate adjusted based on glycemic fluctuation and dose. <u>Non-critically Ill patients</u> • Insulin therapy by basal-bolus regimen is preferred in patients with poor oral intake or NPO • Recommended regimen includes basal, nutritional, correctional components in patients with good nutritional intake <u>T1DM</u> • Pre-meal glucose monitoring only is insufficient (risk hypoglycemia, hyperglycemia, diabetic ketoacidosis <u>Transitioning from Intravenous to Subcutaneous Insulin</u> • First basal insulin dose 1-2 hours before discontinuing intravenous insulin. • Administer 60-80% of the total daily insulin infusion dose as basal insulin <u>Self-Management</u> • Acceptable for patients performing self-management at home, with adequate oral intake, cognitive skills, physical skills, be proficient in carbohydrate estimation, use multiple daily insulin injections or a subcutaneous insulin infusion pump, stable insulin requirements an understand sick day management. • Documentation of self-management should include a protocol approved by the patient, nursing staff and physician.
CDC Clinical Reminder: Insulin Pens Must Never Be Used for More than One Person (Centers for Disease Control and Prevention 2012)[54,55]	Insulin pen: • Insulin pens with multiple doses are for use by a single patient only • Insulin pens should be clearly labeled with the patient's name and identifying information • Hospitals and facilities should educate their staff about safe use of insulin pens • Persons exposed to reuse of an insulin pen should be notified and have appropriate blood-borne pathogen testing

Ongoing Concern About Insulin Pen Reuse Shows Hospitals Need to Consider Transitioning Away from Them (ISMP 2013)[57]	• Ongoing issues with insulin pens – Transition away from insulin pens for routine inpatient use
	  ○ Use of pen on multiple patients
	  ▪ Disease transmission

Draft Guidelines for the Safe Use of Subcutaneous Insulin Across the Continuum of Care (ISMP 2016)[56]	• Specialist consultation for complex insulin needs • Develop protocols, order sets and decision support capabilities for institutional administration and self-management • Use of tall man lettering, entire name of fixed combination insulins • Sliding scale should not be the only method to control hyperglycemia • Insulin pens dispensed for a single patient only

Safer insulin prescribing [NICE KTT20][58]	• People with diabetes
	  ○ should receive information about awareness and management of hypoglycemia
	  ▪ A fast-acting source of glucose should always be available
	  ▪ Severe hypoglycemia with reduced level of consciousness may require glucagon administered by another person
	  ○ must notify the Driver and Vehicle Licensing Agency, if they drive
	  ○ should receive 'sick-day' awareness and rules

Source	Recommendations
	○ should receive training on the differences between and use of high-strength, fixed combination and biosimilar insulins. ○ should use insulin only in the way they have been trained to prevent dangerous overdose or underdose • Adults using insulin should receive a patient information booklet and Insulin Passport (safety card) • Reducing errors; in 2011, 60% of 16,600 insulin-related adverse drug events (including 6 deaths were the result of wrong insulin product, omitted or delayed insulin dose and wrong insulin dose) ○ always spell out the word 'units' ○ use high-strength insulin only with pre-filled syringe supplied in ○ Educate concerning the appearance of different insulins ○ Close monitoring of blood glucose levels when starting high-strength insulin and in the following weeks. ○ Ensure the person is given, reads and understands the educational materials provided with high-strength insulins ○ Use of non-insulin syringes only, marked in units not mL ○ Hospitalized inpatients should be able to self-administer insulin (if feasible and safe) to reduce the harm of incorrect timing with respect to food. • Insulin should never be removed from a prefilled insulin pen • Pharmaceutical manufacturers should not directly contact people with diabetes and urge them to change their device or insulin delivery system

Key: FPG=fasting plasma glucose; A1C=glycosylated hemoglobin; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus; GLP-1 RA=Glucagon-like peptide-1 receptor agonist; NPH=neutral protamine Hagedorn insulin; CSII=continuous, subcutaneous insulin infusion; DKA=diabetic ketoacidosis; SGLT-2=sodium/glucose cotransporter 2 inhibitor; DPP-4=dipeptidyl peptidase 4 inhibitor; CHO=carbohydrate

Pharmacology

Pharmacokinetics and Pharmacodynamics

Neutral Protamine Hagedorn insulin (NPH) suspension was the first long-acting insulin developed by the addition of protamine and zinc to regular insulin.[24,67] NPH displays a slower onset and longer duration of action.[24,67] Although longer-acting, NPH is not an ideal basal insulin as the serum concentration-time curve demonstrates a peak effect with a duration of action of only 12-18 hours. NPH use is associated with increased risks of anytime and nocturnal hypoglycemia.[68] Variability in absorption and duration of action often necessitate administration 2-3 times daily.[69,70] Inadequate re-suspension of NPH insulin may result in variability in absorption and glycemic effects.[24,71] Extended durations of activity were achieved with bovine NPH and ultra-lente insulins but poor and erratic absorption resulting in glycemic swings led to the withdrawal of these products from the US market.[72] Longer-acting, insulin analogues were developed to better mimic the body's basal insulin secretion with longer durations of action, minimal to no peak effect, more consistent absorption and bioavailability, and less risk of hypoglycemia.[24,73] The newer agents, insulin glargine (glargine), insulin detemir (detemir) and insulin degludec (degludec) have many of these properties. Detemir and glargine do not provide 24-hour activity in 40% of T1DM patients.[24,68,74-76]

Insulin glargine is a result of a modification of human insulin though a pH change. Glargine exhibits a different isoelectric point than human recombinant insulin.[67] Injected glargine precipitates as hexamers in tissue after SQ administration. Absorption is delayed, prolonging the duration of action.[42,77-79] Slower absorption leads to steady, peakless serum levels for approximately 24 hours. Glargine is metabolized to M1 and M2 metabolites possessing similar glycemic activity. Glargine may not be directly mixed with other insulins.[79]

Insulin detemir is a result of the acetylation of a fatty acid side chain to human insulin.[67] Protein binding to albumin is increased, prolonging the duration of action to less than 24 hours.[78,79] Detemir may require twice daily dosing to achieve adequate glycemic control in T1DM and T2DM. Detemir may not be directly mixed with other insulins.[79]

Insulin degludec is a recombinant, modified, human insulin that forms multihexamers at the injection site.[79,80] The multihexamers slowly separate and are absorbed. Degludec is a long-acting basal insulin analogue with a half-life of approximately 25 hours and long duration of activity (>42 hours) in

T1DM.[28] Steady state is achieved after 2-3 days of once daily subcutaneous injection. Compared to other basal insulins, insulin degludec produces 4-times less intra-subject variability than glargine, as well as other basal insulins.[24,74,81,82] The package insert states insulin degludec may not be mixed with other insulins, however, a manufacturer premix of insulin degludec and insulin aspart is approved (but not yet marketed) in the United States.[83,84]

Clamp studies in T1DM are the source of most PK/PD information. Insulin glargine and insulin detemir have flatter activity profiles than NPH insulin.[69,85,86] Neither agent is truly peakless. Both demonstrate a gentle increase and decrease in activity with a 24 hour duration of activity. Detemir is associated with lower within-subject variability than glargine or NPH.[85,86] Once-daily administration of glargine and detemir is possible, although twice daily dosing is required in some patients. Due to the 24-hour duration of activity, glargine and detemir require administration at the same time each day. Pharmacokinetic and pharmacodynamic studies with glargine U300 show a flatter, more consistent glucose-lowering effect over a 24-hour period with a duration of activity exceeding 24 hours, low within-day variability, and high between day reproducibility.[87-89] Insulin degludec also has a smooth, stable pharmacokinetic profile with a longer half-life (25 hours) and duration of action (42 hours) allowing for dosing without regard to meals.[81] Insulin degludec provides less inter-individual variability in day-to-day glycemic control than glargine U100.[90] Degludec U100 and U200 formulations are bioequivalent in individuals with T2DM.[42] The pharmacokinetics of the basal insulins are presented in Table 2.

Table 2: Basal Insulin Pharmacokinetics[4,29-32,82,83,87,91]

Generic Name*	Trade Name	Form	Onset (hours)	Peak (hours)	Active Metabolite	Half-Life (hours)	Duration (hours)	RX
Intermediate Acting								
NPH	Humulin® N Novolin® N	Human	2 to 4	6-10	No	4.4	14 to 24	No
Long Acting								
Insulin detemir	Levemir®	Analog	1 to 3	No peak	No	5 to 7	18 to 20 (6 to 23; dose dependent)	Yes
Insulin glargine	Lantus®	Analog	2 to 4	No peak	M1 & M2 metabolites	12.5	20 to 24 (10.8 to > 24)	Yes
Insulin glargine	Basaglar®	Follow-on biologic	2 to 4	No peak	M1 & M2 metabolites	12.5	24	Yes
Ultra-Long Acting								
Insulin glargine U300	Toujeo®	Analog	6	No peak	M1 & M2 metabolites	19	36	Yes
Insulin degludec (U100 and U200)	Tresiba®	Analog	~1	No peak	No	25	42	Yes

Key: *U-100 unless otherwise noted

Special Populations

Ethnic Groups

No difference in pharmacokinetics were noted between African Americans, Hispanics/Latinos or Caucasians for detemir or degludec.[92,93] Dose-response relationships and time-action profiles were similar across ethnic groups.[92,93]

Elderly

No differences in safety or efficacy have been observed in patients ≥65 years in key clinical trials of glargine or detemir.[30,32]

Children and Adolescents

Tresiba® is labeled for use in T1DM and T2DM in pediatrics. Basaglar®, Lantus® and Levemir® are labeled for use in T1DM while use of concentrated insulin glargine, Toujeo® is not established in pediatrics.[29-32,83] The newer basal insulins afford less interpatient and intrapatient pharmacokinetic variability across and within age groups compared with NPH.[94-96] This may reduce the risk of hypoglycemia in children and adolescents. Where approved, dosing and titration in pediatrics is similar to adults.[29-32,83] In the treatment of T1DM, NPH, glargine and detemir produced similar A1C reductions while the insulin analogues resulted in significantly lower FPG.[76,97] Most trials found comparable hypoglycemia risk with NPH and insulin glargine, although one trial found hypoglycemia more frequent with glargine use.[79]

Pregnancy

In pregnant women with T2DM or gestational diabetes in which hyperglycemia remains uncontrolled with diet and lifestyle modifications insulin remains the gold standard treatment. Detemir is indicated in pregnancy (pregnancy category B) while use of other basal insulin requires assessment of risk and benefit. In gestational diabetes, no insulin or insulin regimen has proven superior.[98]

Renal and Hepatic Dysfunction

Renal and hepatic dysfunction are risk factors for hypoglycemia.[99] The basal insulin analogues are not well studied in this setting, however, professional prescribing information for all basal insulin analogues except Tresiba® report increased circulating levels of insulin associated with renal dysfunction.[28-32] Use of any of these agents should include careful monitoring and dosage adjustment in patients with renal or hepatic dysfunction.[28-32]

Clinical Efficacy

Trials were excluded if regarding acute care/hospital care/critically ill; regarding glucose monitoring; regarding insulin pumps/continuous infusion; regarding pen devices vs vial and syringe; not FDA-approved routes of administration (i.e. oral/buccal); combination therapies of DPP4 inhibitors or GLP1 analogues with insulin; use for non-diabetes indications or when full-text of the trial was unavailable for review. Appendix 3 includes the identified systematic reviews, meta-analyses, pooled-evidence and network analysis concerning clinical use of basal insulins in the treatment of type 1 and type 2 diabetes mellitus. Trials are arbitrarily grouped by predominant population and include basal insulin use in T1DM[100-108] insulin-naïve T2DM[101,109,110], basal-oral therapy in T2DM[111], basal or basal/bolus

in T2DM[112-123] T1DM/T2DM combined assessments[124-130], special populations (pregnancy, elderly)[114,131-135], quality of life[115,136], cancer risk[137-144] and cardiovascular morbidity and mortality[145].

Long-acting insulin analogues versus NPH insulin: Three meta-analysis and a Cochrane review compared grouped long-acting analogues (LAA) to NPH. Two were performed in T1DM and two in T2DM patients.[103,108,113,118] In T1DM, both analyses found LAA statistically superior to NPH in reducing A1C values, nocturnal and severe hypoglycemia. The Cochrane review additionally reported superiority of LAA in reduced weight gain and FPG [103,108] In T2DM, both analyses agree that LAA significantly reduce nocturnal hypoglycemia without significant effect on severe hypoglycemia. In analyses defining the specific LAA, detemir statistically reduced weight gain vs NPH in T1DM and T2DM.[103,118] The evidence suggests LAA may afford reductions in anytime or nocturnal hypoglycemia and aid in blood glucose control. Detemir use is associated with less weight gain.

Detemir versus NPH: A total of 9 meta-analysis, network meta-analysis, pooled-post hoc analysis, and Cochrane review evaluated the use of detemir with NPH in T1DM and T2DM.[103-107,114,129,146] Detemir use resulted in a statistically significant reduction in weight gain.[103,106,107,114,117,129,146] Detemir demonstrated A1C lowering effects at least as effective as NPH with three analyses finding detemir significantly superior.[106,107,147] Evidence is inconclusive for FPG effects and insulin dosage. In T1DM, the incidence of any hypoglycemia with detemir did not differ from NPH although symptomatic, nocturnal and severe hypoglycemia were significantly lower with detemir in one report.[103-107] One analysis reported on adverse outcomes.[105] More withdrawals due to adverse events occurred with detemir while more withdrawals due to a lack of efficacy were found with NPH.[105] Overall, detemir use resulted in similar glycemic effects, lower weight gain and lower rates of overall and nocturnal hypoglycemia.

Detemir versus glargine: Detemir was compared with glargine in 6 meta-analysis or Cochrane reviews.[104,105,111,117,122,123] Detemir consistently and statistically reduced weight gain associated with insulin therapy.[111,117,122,123] A1C levels were similar with use of daily detemir or glargine, however, when detemir was dosed twice daily it resulted in superior A1C reductions versus daily glargine.[104,105] Two reports included information concerning FPG and insulin doses.[122,123] Results were similar in the meta-analysis, while the Cochrane review found glargine superior in reducing FPG at lower insulin dosage requirements.[122] The incidence of hypoglycemia was similar between agents for overall, nocturnal and severe classifications. Detemir ± oral therapy was associated with more withdrawals due to adverse events and more injection site reactions than glargine ± oral therapy.[122,123] Treatment of T1DM and T2DM with detemir vs glargine required 38% higher detemir dosages in a systematic review of 7 large RCTs (range 8-77.2%).[148] Twice daily dosing of detemir may be required in T1DM patients, at doses ≤0.4 units/kg/day, and when glucose control appears to decline after 12 hours.[148] Swinnen et al,[122] reported detemir was dosed twice-daily in 13-57% of subjects. Treatment satisfaction was higher with glargine therapy.[111] Overall, glucose control and hypoglycemia risk were similar in T2DM treated with detemir or glargine.[149-153] In T1DM, detemir was associated with a lower incidence of severe and nocturnal hypoglycemia although detemir patients were less likely to have achieved glycemic control and more patients required twice daily dosing.[67,154] Overall, detemir may reduce weight gain but often requires twice daily dosing.

Glargine versus NPH: A total of 14 meta-analysis, meta-regression analysis, pooled analysis and Cochrane review compared glargine to NPH in T1DM, T2DM and pooled T1DM/T2DM.[102,104,105,107,109-112,116-118,121,126,129] A significant reduction in weight gain was found more commonly with NPH than

glargine in T2DM.[109,110,112] Glargine use resulted in lower A1C levels than NPH in 5 or 11 reports with the remaining trials finding no difference.[104,105,107,155] Of note, A1C reductions were more common with glargine monotherapy in T2DM in people with a longer duration of diabetes.[110,111] Glargine and NPH doses were similar, with two trials reporting significantly lower NPH doses.[109,110] Glargine use was associated with significant reductions in nocturnal hypoglycemia, severe nocturnal hypoglycemia and symptomatic hypoglycemia. Reports differed with 50% reporting glargine superior in reducing overall hypoglycemia. Severe hypoglycemia was significantly lower with glargine compared with NPH in 4 of 10 analyses.[109,121,126,155] Reports of injection site pain were 4-times more frequent with glargine than NPH (2.7% vs. 0.7%).[156] Patient satisfaction was higher with glargine + oral medications compared with NPH + oral medications.[111] Overall, glargine is associated with less hypoglycemia than NPH insulin.

Degludec versus glargine: Comparison of degludec and glargine was performed in 6 meta-analysis.[101,124,127,130,157,158] Degludec was found noninferior to glargine for measures of A1C.[124,130,158] Degludec was found superior to glargine in reducing FPG levels.[130,158] In the single analysis that presented insulin dosage information, degludec doses were significantly less than glargine in T1DM, T2DM and type 2 insulin naïve patients.[130] Degludec consistently and significantly reduced the risk of hypoglycemia (overall, nocturnal and severe) compared with glargine in trials of T1DM, T2DM, insulin naïve T2DM, basal-bolus therapy and during both trial and maintenance periods. Two quality of life meta-analysis evaluated therapy with degludec or glargine.[136,159] These analysis found that degludec therapy was associated with a statistically significant improvement in both mental and physical health status as well a significant, modest improvement in health utility. [136,159] It is likely that the extended duration of action of degludec producing more consistent glycemic control contributes to the efficacy and safety outcome superiority over glargine.

Degludec versus detemir: Evidence comparing degludec with detemir comes from two randomized, controlled trials in T1DM. Degludec resulted in a significantly lower risk of nocturnal hypoglycemia and greater weight gain than detemir.[160,161]

Degludec versus other LAAs: Two meta-analysis provide information concerning degludec versus other LAA, one performed in T1DM and another in T1DM/T2DM.[100,125] Degludec produced similar weight and A1C changes. One of the trials found degludec statistically superior to LAA in reducing FPG and anytime hypoglycemia. Both analyses found degludec superior in reducing nocturnal hypoglycemia. In T1DM, a statistically lower degludec dose was required, whereas in combined T1DM/T2DM a higher degludec dose was required.[125] This may reflect the prevalence of insulin resistance in T2DM.

Degludec trials must be interpreted with caution.[24] Most trials targeted a FPG of <90 mg/dL and may not be generalizable to real-world practice. Degludec was administered with the evening meal while glargine was administered any time of the day. The definitions of hypoglycemia and severe hypoglycemia did not match the ADA criteria, although statistical significance remained in most trials after reanalysis using ADA criteria.[162]

Concentrated Insulins

Glargine U300 (Toujeo®) versus U100: In the treatment of T2DM, meta-analysis comparing glargine U300 to glargine U100 found the concentrated U300 preparation to significantly reduce weight gain while providing similar A1C and FPG effects.[120] The dose of U300 was 12% higher than U100.[120]

Glargine U300 was statistically superior to U100 in producing less hypoglycemic episodes, symptomatic hypoglycemia, nocturnal hypoglycemia and severe hypoglycemia.[120] The NNT to prevent one case of severe or confirmed hypoglycemia was 16.[120] Randomized trials found nocturnal or any-time hypoglycemia occurred similarly with glargine U300 and U100 in T1DM.[163,164] Nocturnal hypoglycemia was reduced during the first 8-weeks of treatment (when hypoglycemia is more common).[163] Meta-analysis found a reduction in nocturnal hypoglycemia in T2DM trials.[165-167] An extension trial found no difference in anytime hypoglycemia between U300 and U100 glargine.[167] Nocturnal or any-time hypoglycemia occurred similarly with glargine U300 and U100 and in T1DM.[163,168] Nocturnal hypoglycemia was reduced with U300 vs U100 glargine during the first 8-weeks of treatment.[163] A reduction in nocturnal hypoglycemia was also found in T2DM trials.[165-167] No difference was reported for anytime hypoglycemia between U300 and U100 glargine, but U300 glargine use resulted in a reduction in nocturnal hypoglycemia.[169] Use of glargine U300 versus U100 resulted in significantly less hypoglycemia, especially nocturnal.[77,170]

Glargine U300 versus detemir or degludec: In meta-analysis comparing glargine U300 to degludec or detemir, most trials involved basal-oral therapy.[115,136] No differences were reported between U300 and detemir or degludec for weight change, insulin dose or development of any or nocturnal hypoglycemia. Detemir trials found a significant reduction in A1C with U300 glargine use.[115]

Special Populations

Gestational Diabetes: Evidence included 3 systematic review/meta-analyses and a randomized controlled trial evaluating diabetes in pregnancy and maternal and fetal safety. Evaluated agents included glargine, NPH, and detemir.[131-134] Overall, no differences were found between basal insulins for glycemic efficacy, hypoglycemia and maternal or fetal outcomes.[131-134] Use of detemir-BB vs NPH-BB in a RCT did find detemir superior in reducing FPG at 24- and 36-gestational weeks.[133]

Elderly: A meta-analysis and a pooled-analysis evaluated the use of basal insulin in the elderly.[135] The meta-analysis of 7 trials comparing degludec with glargine included 917 adults age >65 years.[135] The proportion of patients with confirmed hypoglycemia did not differ among T1DM or T2DM patients although the proportion with hypoglycemia was higher in T1DM patients (T1DM 94.1%-97.7% vs T2DM 58.7% for both agents).[135] In T2DM, treatment with degludec resulted in significantly less overall confirmed and nocturnal confirmed hypoglycemia. In T1DM, degludec use resulted in significantly fewer cases of nocturnal confirmed hypoglycemia. Over the maintenance period of the included trials, the agents performed similarly.[135] All trials were funded by Pharma and patients were excluded with hypoglycemic unawareness, serious comorbidity or a history of more than one episode of severe hypoglycemia. The pooled data analysis comparing detemir with NPH in the elderly, found detemir significantly reduced all and symptomatic hypoglycemic episodes while nocturnal episodes did not differ.[114] Detemir use significantly reduced weight gain. Mean insulin dosages were similar.[114]

Safety

Monitoring[2,171]

Monitoring of insulin therapy includes periodic determination of A1C levels. Achieving glycemic control (A1C targets) is indicative of efficacy. Monitoring is similar with insulin degludec, insulin determir and insulin glargine. In patients meeting A1C goals, monitor twice yearly. In patients not meeting A1C

goals or during therapy changes, monitor A1C every 3 months or more often, as indicated. Self-monitoring of blood glucose should be performed as needed for patients receiving a single daily injection of basal insulin therapy, to meet goals. Patient's receiving multiple daily injections (or pump therapy) should monitor blood glucose at least 3 times a day; prior to meals and snacks, at bedtime, occasionally postprandially, prior to exercise/critical tasks, upon suspicion of hypoglycemia and if hypoglycemic, until normoglycemic. Additional blood glucose monitoring may be required in pediatric, pregnant, renally/hepatically impaired patients, during times of stress, illness, changes in therapy (including insulin dosage, manufacturer or method of administration), with co-administration of interacting medications, changes in meal patterns and in patients at higher risk of hypoglycemia or reduced awareness of hypoglycemia. Monitoring potassium levels in patients at risk of hypokalemia is recommended for insulin degludec and insulin glargine. Monitoring for signs and symptoms of heart failure is recommended for patients receiving insulin glargine and a thiazolinedione.

Adverse Events

The most common adverse event reported with use of basal insulin analogues is hypoglycemia. Use of any insulin may be associated with hypersensitivity and allergic reactions (which may include anaphylaxis), injection site reactions, lipodystrophy, development of immunogenicity (anti-insulin antibodies), peripheral edema and weight gain.[2,29-32,83,171-173] Overall, no significant differences in non-hypoglycemic adverse events are noted among the basal insulin analogues. [2,29-32,83,171] Table 4 compares the adverse event profiles of the basal insulin analogues.

Table 3: Comparison of Long-acting Basal Insulin Adverse Reactions[2,28-32,171,173]

	Adverse Event Rates >10%	Adverse Event Rates 1 to 10 %
Basaglar® Insulin glargine	**Cardiovascular:** Hypertension (20%), peripheral edema (20%) **Central nervous system**: Depression (11%) **Endocrine & metabolic:** Hypoglycemia (Type I on combination regimens: ≤69%; Type II on combination regimens: ≤8%; monotherapy in adults ≥50 years old: 6% [ORIGIN trial]) **Gastrointestinal:** Diarrhea (11%) **Genitourinary:** Urinary tract infection (11%) **Immunologic**: Antibody development (20% to 44%; effect on therapy not reported) **Infection:** Influenza (19%), infection (9% to 14%) **Neuromuscular & skeletal:** Arthralgia (14%), back pain (13%), limb pain (13%) **Ophthalmic**: Cataract (18%), retinopathy (14%) Respiratory: Upper respiratory tract infection (adults: 6% to 29%; children & adolescents: 14%), sinusitis (19%), bronchitis (15%), nasopharyngitis (7% to 13%), cough (12%)	**Cardiovascular**: Retinal vascular disease (6%) **Central nervous system:** Headache (6% to 10%) **Local:** Pain at injection site (3%) **Respiratory:** Pharyngitis (children & adolescents: 8%), rhinitis (children & adolescents: 5%) **Miscellaneous:** Accidental injury (6%) Frequency not defined: **Endocrine & metabolic**: Sodium retention **Local:** Erythema at injection site, itching at injection site, localized edema, swelling at injection site **<1%, postmarketing, and/or case reports:** Anaphylaxis, angioedema, bronchospasm, hyperglycemia, hypersensitivity reaction, hypertrophy at injection site, hypokalemia, hypotension, injection site reaction (including urticaria and inflammation), lipoatrophy at injection site, lipoatrophy at injection site, shock, skin rash, weight gain
Lantus® Insulin glargine	**Cardiovascular**: Hypertension (20%), peripheral edema (20%) **Central nervous system:** Depression (11%) **Endocrine & metabolic**: Hypoglycemia (Type I on combination regimens: ≤69%; Type II on combination	**Cardiovascular:** Retinal vascular disease (6%) **Central nervous system:** Headache (6% to 10%) **Local:** Pain at injection site (3%)

	Adverse Event Rates >10%	Adverse Event Rates 1 to 10 %
	regimens: ≤8%; monotherapy in adults ≥50 years old: 6% [ORIGIN trial]) **Gastrointestinal**: Diarrhea (11%) **Genitourinary:** Urinary tract infection (11%) **Immunologic:** Antibody development (20% to 44%; effect on therapy not reported) **Infection:** Influenza (19%), infection (9% to 14%) **Neuromuscular & skeletal:** Arthralgia (14%), back pain (13%), limb pain (13%) **Ophthalmic:** Cataract (18%), retinopathy (14%) **Respiratory:** Upper respiratory tract infection (adults: 6% to 29%; children & adolescents: 14%), sinusitis (19%), bronchitis (15%), nasopharyngitis (7% to 13%), cough (12%)	**Respiratory:** Pharyngitis (children & adolescents: 8%), rhinitis (children & adolescents: 5%) **Miscellaneous:** Accidental injury (6%) Frequency not defined: **Endocrine & metabolic:** Sodium retention **Local:** Erythema at injection site, itching at injection site, localized edema, swelling at injection site **<1%, postmarketing, and/or case reports**: Anaphylaxis, angioedema, bronchospasm, hyperglycemia, hypersensitivity reaction, hypertrophy at injection site, hypokalemia, hypotension, injection site reaction (including urticaria and inflammation), lipoatrophy at injection site, lipoatrophy at injection site, shock, skin rash, weight gain
Toujeo® Insulin glargine	**Cardiovascular**: Hypertension (20%), peripheral edema (20%) **Central nervous system:** Depression (11%) **Endocrine & metabolic**: Hypoglycemia (Type I on combination regimens: ≤69%; Type II on combination regimens: ≤8%; monotherapy in adults ≥50 years old: 6% [ORIGIN trial]) **Gastrointestinal**: Diarrhea (11%) **Genitourinary:** Urinary tract infection (11%) **Immunologic**: Antibody development (20% to 44%; effect on therapy not reported) **Infection**: Influenza (19%), infection (9% to 14%) **Neuromuscular & skeletal:** Arthralgia (14%), back pain (13%), limb pain (13%) **Ophthalmic:** Cataract (18%), retinopathy (14%) **Respiratory**: Upper respiratory tract infection (adults: 6% to 29%; children & adolescents: 14%), sinusitis (19%), bronchitis (15%), nasopharyngitis (7% to 13%), cough (12%)	**Cardiovascular:** Retinal vascular disease (6%) **Central nervous system**: Headache (6% to 10%) **Local:** Pain at injection site (3%) **Respiratory:** Pharyngitis (children & adolescents: 8%), rhinitis (children & adolescents: 5%) **Miscellaneous:** Accidental injury (6%) **Frequency not defined:** **Endocrine & metabolic:** Sodium retention **Local:** Erythema at injection site, itching at injection site, localized edema, swelling at injection site **<1%, postmarketing, and/or case reports**: Anaphylaxis, angioedema, bronchospasm, hyperglycemia, hypersensitivity reaction, hypertrophy at injection site, hypokalemia, hypotension, injection site reaction (including urticaria and inflammation), lipoatrophy at injection site, lipoatrophy at injection site, shock, skin rash, weight gain
Levemir® Insulin detemir	**Central nervous system:** Headache (adults: 7% to 23%, children: 31%) **Endocrine & metabolic:** Hypoglycemia (Type 1 combination regimens: children & adolescents: 93% to 95%, adults: 82% to 88%; Type 2 combination regimens: adults: 9% to 41%), severe hypoglycemia (Type 1 combination regimens: children & adolescents: 2% to 16%; adults 5% to 9%; Type 2 combination regimens: adults: ≤2%) **Gastrointestinal:** Gastroenteritis (children & adolescents: 17%), abdominal pain (6%; children & adolescents: 13%) **Respiratory:** Upper respiratory tract infection (13% to 26%; children & adolescents: 36%), pharyngitis (10%; children & adolescents: 17%), flu-like symptoms (8%; children & adolescents: 14%)	**Gastrointestinal:** Nausea (children & adolescents: 7%), vomiting (children & adolescents: 7%) **Infection:** Viral infection (children & adolescents: 7%) **Respiratory:** Cough (children & adolescents: 8%), rhinitis (children & adolescents: 7%) **Miscellaneous:** Fever (children & adolescents: 10%) **<1%, postmarketing, and/or case reports:** Pain at injection site

	Adverse Event Rates >10%	Adverse Event Rates 1 to 10 %
Tresiba® Insulin degludec	**Frequency not always defined.** **Cardiovascular:** Peripheral edema (1% to 3%) **Central nervous system**: Headache (9% to 12%) **Endocrine & metabolic:** Severe hypoglycemia (10% to 13%, type 1 diabetics on combination therapy; ≤5%, type 2 diabetics on combination therapy), antibody development, hypoglycemia, hypokalemia, weight gain **Gastrointestinal**: Diarrhea (6%, type 2 diabetes), gastroenteritis (5%, type 1 diabetes) **Local**: Injection site reaction (4%; including hematoma, pain, hemorrhage, erythema, warmth, swelling, mass, nodules, and discoloration), hypertrophy at injection site, lipoatrophy at injection site **Respiratory:** Nasopharyngitis (13% to 24%), upper respiratory tract infection (8% to 12%), sinusitis (5%, type 1 diabetes)	**<1%, postmarketing and/or case reports:** Hypersensitivity reaction

Hypoglycemia

Hypoglycemia (blood glucose<50 mg/dL) is reported at least annually in 7% to 15% of insulin-treated patients, with 1-2% reporting severe hypoglycemia.[51] On average, patients with T1DM experience two symptomatic hypoglycemic episodes weekly and one severe, temporarily incapacitating episode yearly.[99] In T2DM, the incidence is lower initially, but as disease duration increases and beta-cell function fails, the incidence approaches that of T1DM.[78,99]

Hypoglycemia is defined the by 1) the development of neurogenic/autonomic symptoms (trembling, shakiness, palpitations, sweating, anxiety, hunger, nausea, tingling) or neuroglycopenic symptoms (difficulty concentrating, confusion, weakness, drowsiness, vision changes, difficulty speaking, headache, dizziness); 2) a plasma glucose level below or 72 mg/dL in the presence of insulin or insulin secretagogue therapy; and 3) symptoms responsive to carbohydrate administration.[14,49,64,174,175] Clinical manifestations define the severity of hypoglycemia, *mild*: autonomic symptoms in a patient able to self-treat; *moderate*: autonomic and neuroglycopenic symptoms in a patient able to self-treat; *severe*: the individual may be unconscious, requires the assistance of another person and is often associated with plasma glucose levels below 54 mg/dL.[64] Hypoglycemia may affect work or driving over the short-term and produce neurological symptoms with prolonged coma over the intermediate-time. Long-term and severe hypoglycemia may lead to mild and permanent cognitive and neurologic sequelae. Recurrent hypoglycemia impairs the ability to sense future episodes. Some evidence suggests frequent, severe hypoglycemia is associated with small (but perhaps clinically meaningful) decreases in intellectual performance.[47,49,174,175] Hypoglycemia in T2DM is associated with a 2 to 4-times higher death rate.[51]

Meta-analysis suggest that microvascular complications and not hypoglycemia, *per se*, are responsible for the cognitive changes in patients with type 1 diabetes. In contrast, evidence suggests T2DM patients with severe hypoglycemia requiring hospital care have an increased risk for developing dementia. Symptomatic hypoglycemia is associated with an increased mortality rate in T2DM patients

with established or very high risk for cardiovascular disease. The mechanism remains ill-defined but may include hypoglycemia-induced inflammation or cardiac conduction effects. Overall, it is believed sympathetic effects and not glycemic effects are responsible for the cognitive changes associated with hypoglycemia.[14,49,59,99]

Individuals with diabetes receiving insulin therapy develop hypoglycemia for a variety of reasons. No currently available insulin product or insulin dosage regimen perfectly matches normal human insulin secretion and hypoglycemia (as well as hyperglycemia) may result.[24,69,176,177] Caloric intake may be inadequate for the insulin dose due to reduced intake, increased exercise, catabolic stress (e.g. infection, myocardial infarction), decreased gluconeogenesis, reduced insulin elimination via impaired renal function in chronic kidney disease, end-stage kidney disease or acute kidney injury, increased insulin dose, unintentional medical error or intentional error (e.g. self-harm, homicide)[175,178]

Risk factors for hypoglycemia in T1DM, include prior episode(s) of severe hypoglycemia, low A1C (<6%) levels, hypoglycemia unawareness, longer duration of diabetes, autonomic neuropathy, adolescence and preschool age children unable to detect or self-treat hypoglycemia.[14,49,174,175] Risk factors for hypoglycemia in T2DM, include older age, severe cognitive impairment, poor health literacy, food insecurity, increased A1C, hypoglycemia unawareness, duration of insulin therapy, renal impairment and neuropathy. Hypoglycemia risk in T2DM is also increased in women with established CV disease, or age >54 years with two cardiovascular disease (CVD) risk factors. Risk factors for severe hypoglycemia, include prior hypoglycemic episode, A1C <6%, hypoglycemia unawareness, long-duration of insulin therapy, autonomic neuropathy, low socioeconomic status, food insecurity, low health literacy, cognitive impairment, adolescence and preschool age children unable to detect or self-treat mild hypoglycemia.[14,49,174,175] The elderly with diabetes are at particular risk of hypoglycemia.[51,179,180] Geriatric risk factors include renal insufficiency, preexisting and progressing cognitive deficits that may affect self-care and contribute to administration issues.[61,180] Targeted glycemic control in the elderly depends upon clinical and cognitive factors, social difficulties, functional dependency, living situation and life expectancy. A1C targets may range from <7.5% in healthy elderly with long(er) life expectancy to <8.5% for complex patients with limited life expectancy.[61,180]

For any individual with a case of clinically significant hypoglycemia, glycemic targets should be raised for at least several weeks to reverse hypoglycemia unawareness and reduce the risk of future episodes.[14]

Meta-analysis of A1C treats-to-target trials found that long-acting basal insulin analogues are associated with lower rates of nocturnal and symptomatic hypoglycemia. The risk of hypoglycemia is lower with use of insulin degludec than insulin glargine or insulin detemir.[101,124,127,130,157,158,161,181] One meta-analysis found no difference in the incidence of any-time, or nocturnal hypoglycemia with insulin glargine concentrations U-300 or U-100.[120]

The treatment of individuals with diabetes requires the balancing of glycemic control with the avoidance of hypoglycemia. For this reason, A1C targets should be individualized, based on diabetes duration, age/life expectancy, comorbid conditions, known cerebrovascular disease or microvascular complications, risk of hypoglycemia, adverse consequences of hypoglycemia, patient motivation and adherence.[15,16]

Cardiovascular Safety

Insulin receptors line the vascular walls.[67] Insulin acts to produce vasodilation via intrinsic kinase activity, endothelial nitric oxide synthase, reductions in vascular tone and smooth muscle proliferation, reduced adhesion of inflammatory cells and platelet aggregation, and less production of reactive oxygen molecules. Insulin can also result in vasoconstriction by activating the mitogen-activated protein kinase (MAPK) cascade and induce endothelial cell growth. In individuals without diabetes, insulins acts to produce vasodilation; while in the setting of insulin resistance, vasoconstrictive properties predominate.[67]

Epidemiological studies in T2DM found a higher risk of cardiovascular events in patients treated with insulin compared with other therapies.[182] Patients treated with insulin tend to be older, with longer duration of diabetes and more comorbidities and complications. If patients who use insulin have more severe disease, the observational data is no longer valid as statistical analysis cannot account for severity of disease.[67]

Overall, the cardiovascular risk associated with use of human or analogue insulin remains ill-defined. The available evidence must be interpreted with caution. In the DIGAMI 1 (Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction) trial, insulin reduced mortality, but it is unclear whether this reflects the effect of improved glucose control or a glucose-independent action.[183] The DIGAMI 2 trial was intended to evaluate cardiovascular outcomes stratified by different glycemic endpoints but all patients showed similar glucose control in spite of different glycemic targets.[184] A trial evaluated insulin-sensitizing therapy (metformin ± thiazolidinedione) vs insulin-providing therapy (insulin ± sulfonylurea) in T2DM patients with ischemic heart disease. Five year cardiovascular mortality and myocardial infarction rates did not differ significantly although interpretation is confounded because each of the additional drugs carries its own effects on cardiovascular risk (metformin reduces risk, sulfonylureas and thiazolidinediones may increase risk).[185] The UK Prospective Diabetes Study was underpowered to assess the cardiovascular effects of insulin during the core phase. Cardiovascular morbidity and mortality of insulin therapy was higher than metformin and lower than sulfonylureas.[186] Followup at 10-years identified a significant reduction in myocardial infarction and cardiovascular mortality with insulin therapy. The ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial found no difference in cardiovascular outcomes in patients with recent onset diabetes given glargine vs no therapy or oral therapy. As with all other trials, this trial must be interpreted cautiously as glargine was not compared to NPH or other basal insulin and the mean dose of glargine was very low, 0.4 U/kg. The effects of more commonly used, higher dosages, remains unknown.[187] Evidence suggests that hypoglycemia itself is associated with poor cardiovascular outcomes, perhaps from adrenergic mediated QT prolongation, abnormal myocardial repolarization, ventricular arrhythmias or myocardial ischemia.[188] The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial targeting aggressive blood glucose control resulted in a high incidence of severe hypoglycemia and cardiovascular mortality.[189] A systematic review summarizing the literature concerning cardiovascular morbidity and mortality associated with insulin therapy in T2DM included 8 trials of over 100,000 persons.[145] Significant heterogeneity prevented a quantitiative synthesis of the data. No difference in cardiovascular risk was found between fixed versus variable insulin regimens, or prandial vs basal regimens. Confidence intervals were wide with increased and decreased cardiovascular risk reported.[145]

Basal Insulin Analogues: Insulin receptor binding affinity varies among the basal insulin analogues. Glargine and its metabolite bind at 80%, detemir at 46%, and degludec at 14%.[67] Mitogen-activated protein kinase (MAPK) phosphorylation and intracellular signaling properties also differ among the analogues.[67] Meta-analysis found the risk of severe hypoglycemia compared to NPH insulin is 30% lower with glargine and 50% lower with determir.[117] If hypoglycemia translates to an increased risk of cardiovascular morbidity and mortality, the newer basal insulins should have a favorable cardiovascular risk profile. The ORIGIN trial suggests that glargine is safe at low doses.

Degludec produces the lowest rate of hypoglycemia among the basal insulins. Data submitted to the FDA revealed an increased risk of the composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and unstable angina with degludec vs comparators (estimated hazard ration 1.29, 95% confidence interval 0.88-1.88).[67] The FDA further analyzed the data, omitting patients with unstable angina pectoris (USA) and found a higher rate of cardiovascular risk (incidence rates 1.41 per 100 events per patient per year for degludec or degludec/aspart compared with 0.90 per 100 events per patient year with the comparator). Data was further analyzed excluding USA and including outcome data for 30 days after degludec discontinued and prior therapy (usually glargine) initiated. This analysis yielded a hazard ratio of 1.61 (95% CI 0.99-2.6) for degludec regimens vs comparators.[67] The reason(s) for these various analyses which differ from the predefined analysis plan for approval of diabetes drugs is unclear.

An unanswered question concerning insulin degludec is the effects of overinsulinization and long-term cardiovascular effects. Whereas insulin glargine or NPH administration yield plasma insulin levels of 50-200 pmol/L, insulin degludec yields total plasma concentrations of 6000 pmol/L in patients with type 2 diabetes.[190] A 38-month trial comparing cardiovascular outcomes with degludec to glargine in T2DM was completed September 2016 and results are expected in the next few years.[191]

Mitogenicity

Relationships exists between cancer and exogenous insulin use, diabetes, obesity, insulin resistance and hyperinsulinemia although studies report conflicting results with respect to the cancer risk of long-acting insulin analogues.[190,192-195] Binding to human insulin-like growth factor receptor (hIGF-IR) is associated with mitogenic potency.[196] Glargine binding potency to hIGF-IR is 6.5 x greater than human insulin but each binds with the same residence time.[197] Glargine is quickly transformed to its M1& M2 metabolite, which have lower affinity for hIGF-IR than either glargine or human insulin.[198] Detemir and degludec bind to hIGF-IR with less potency than glargine. Detemir and degludec have not exhibited increased mitogenic activity.[32,199]

Various studies suggest the use of glargine is associated with a greater risk than human insulin for the development of cancer.[125,137-139,141-144,200-202] Increased incidence of breast, pancreas, prostate and any cancer were reported in meta-analyses.[137,139,140,142] These analyses also found a reduction in colorectal cancers with glargine use.[139,142,143] The duration of the studies were often too short to determine if the cancer was caused by glargine or if glargine may increase the growth of a preexistent cancer.[203] A recent study in Finland examining all-cause and cause-specific mortality in 23,751 individuals with diabetes found lower rates of cancer with detemir and glargine than NPH insulin use. With NPH as the reference, the adjusted harms ratio (HR) for detemir was 0.23 (95% CI, 0.14 to 0.40), and for glargine 0.35 (95% CI, 0.22 to 0.54).[204] Compared to glargine, the HR for detemir was 0.67 (95% CI, 0.38 to 1.18).[204]

The American Diabetes Association (ADA)[205], American Association of Clinical Endocrinologists (AACE)[206] and European Association for the Study of Diabetes (EASD) suggest that the current evidence is unclear.[207] The ADA encourages patients to continue to take their insulin and discuss concerns with their providers.[205] The AACE commented on the contradictory findings among generally short-term trials of non-comparable populations, and recommends no change to a patients insulin therapy.[206] EASD also recommends a continuation of insulin therapy until the results of the current studies are confirmed or refuted. Overall, the evidence concerning glargine is fraught with methodological and statistical issues. Nonetheless, the benefit of insulin use in individuals with diabetes remains greater than the risk for cancer. More sound scientific evidence is required.

Tolerability

Patient bulletin boards, suggest injection with Levemir® stings less than Lantus®[208,209]. Higher rates of stinging/injection site reactions with Lantus® may occur because of the difference in pH between Lantus® (pH 4.0) and Levemir® (pH neutral). Conversely, injection site reactions were more common with insulin detemir than insulin glargine (4.5% vs 1.4%) and more adverse events and withdrawals from therapy occurred with detemir than glargine.[149] A trial in pediatric patients reported no difference in pain associated with the injection of NPH or insulin glargine.[210]

Weight Gain

Insulin therapy is often associated with a weight gain of 8.8-11.0 pounds.[211] Weight gain may affect tolerance, adherence and compliance with therapy.[78] In clinical trials, detemir is associated with a weight-sparing effect. The mechanism of reduced weight gain with detemir remains unknown. Findings from meta-analyses found significantly less weight gain with detemir than NPH in T1DM[69,103,106,107] and T2DM[114]. In T2DM, detemir weight gain was less than glargine[122,123] with a single network meta-analysis finding glargine superior to detemir in reduced weight gain.[107] Glargine was associated with significantly less weight gain than NPH in T1DM[107], while NPH weight gain was reported lower than glargine in two meta-analyses in T2DM[110,112]. Weight gain associated with the use of glargine U300 was statistically less than with glargine U100 in T2DM.[120] Randomized, controlled trials report similar or less weight gain with concentrated basal insulins than to U100. Insulin degludec U200 increased weight nonstatistically vs U100. In T1DM insulin glargine U300 resulted in less weight gain than U100.[163] Likewise in T2DM, glargine U300 and U100 produced similar weight gain over 12 months of treatment.[166] Weight gain with insulin is common and detemir has the most favorable effect in limiting weight gain.

Injection Fears

Each of the basal insulins is available in a disposable pen for administration. Compared with the use of vials and insulin syringes, pens are more portable, easier to use, and do not require resuspension (as NPH).[78] The currently available basal insulins are more commonly administered once daily than NPH, offering a less complex insulin regimen. Use of insulin pens may increase patient acceptance improving patient satisfaction and adherence to treatment.[78]

Adherence

An improvement in adherence reduced the risk of hospitalization or emergency department (ED) visits by 13% in 135,649 patients with prescriptions for diabetes treatment compared with nonadherent patients.[37] Those who were initially adherent and became nonadherent were found to

have a 15% increased risk of hospitalization or ED visit compared to continuing adherent patients.[37] Pooled data from 3 retrospective, observational trails evaluated persistence of insulin therapy in 4084 persons with T2DM where therapy advanced from oral medications to the inclusion of a basal insulin (glargine or detemir) and reported persistence at 1-year followup of 65.0%. Higher persistence was associated with older age, initiation of glargine using vial/syringe or disposable pens, or baseline exenatide or sitagliptin use. Persistence resulted in lower A1C values, A1C reductions from baseline and lower health care utilization at follow-up.[212]

Adherence is improved when patients emotional well-being is considered and they understand the treatment regimen and benefit (especially for complex regiments), adverse events and medication costs.[38] Adherence may be improved by lessening regimen complexity, hypoglycemia risk and adverse reactions.[38] Adherence may be improved when the fear of hypoglycemia and incidence of hypoglycemia are reduced. This also allows for insulin dosages to be increased to achieve target A1C goals with improved long-term outcomes.[78]

Simplification of insulin regimens with reductions in the number of daily injections increases adherence. In this regard, use of detemir may be considered less preferred as it is the only basal insulin analogue with prescribing information for once- or twice-daily dosing. Trials submitted to the FDA for approval in T1DM compared twice-daily detemir to daily glargine, daily detemir to daily NPH and twice-daily detemir to twice-daily NPH. In T2DM, twice-daily detemir was compared with twice-daily NPH and in a second trial once- or twice-daily detemir was compared to once- or twice-daily NPH. In all trials, comparable reductions in A1C and fasting plasma glucose (FPG) were noted. Twice daily dosing of glargine was reported in 32.9% with T1DM and 13% with T2DM compared with detemir, 62.5% in T1DM and 48% in T2DM.[42,213-215] In contrast, some practitioners suggest that once-daily dosing of detemir should be the preferred regimen based on clinical evidence.[216,217]

Duplication of Therapy

There is currently no indication for the use of combined basal insulin analogues.

Misuse

Insulin has been misused as a performance-enhancing agent.[218] Psychiatric misuse of insulin, includes attempted and completed suicides, factitious hypoglycemia, Munchausen syndrome by proxy, and illicit use by substance abusers.[219] Patients, particularly young women with T1DM may omit doses of insulin to lose weight.[220]

Medication Errors

Insulin glargine U300 and U100 by Sanofi Aventis (Toujeo® and Lantus®) are available in similar pens with the U300 glargine pen white and green, with the concentration highlighted in orange to distinguish it from U100 glargine. No conversion in dosing is needed. Both U300 and U100 pens are marked in units. An individual need only dial the prescribed dose.[29,30] Should an error occur and a full pen dose be injected, Tresiba® U200 will administer 160 units while all other pens will administer 80 units. Pen needles should never be used on more than one patient even if the needle is changed.[54,56,57]

A number of medication errors are associated with the use of needle and syringe administration of insulin from vials[221];

- Misinterpretation of U-100 on a vial to mean the vial includes 100 units of insulin. Availability in 10 mL vials makes large dose errors possible. In institutions, stocking the smallest vial size may be preferred.
- Measuring the dose in units incorrectly in a non-insulin syringe as mL (e.g. 4 units = 4mL)
- Confusion in using concentrated insulin and calculating conversions for use in syringes marked in units.
- In an institutional setting, manufacturer vials may look similar
- Use of the same syringe to administer insulin products that should not be mixed

Drug Interactions

Drug interaction potential among the basal insulins is similar in producing hyperglycemia, hypoglycemia, variable glycemic response, or masking/blunting the signs or symptoms of hypoglycemia.[29-32,83] Detemir exhibits strong, reversible binding to albumin but does not interact with other highly bound medications (e.g. warfarin, ibuprofen, diazepam, valproate).[197] All basal insulins interact to increase blood glucose levels in combination with glucocorticoids, typical antipsychotics, oral contraceptives, protease inhibitors, diuretics, phenytoin and sympathomimetics. A decrease in blood glucose may be associated with use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers and high-dose salicylates. Combination with alcohol may increase or decrease blood glucose levels.[2,171,173]

Storage

All basal insulin are available in pens for administration. Lantus and Levemir are also available in vials. Table 3 presents the basal insulin storage requirements. Unopened, storage at room temperature is longest with degludec (56 days), followed by detemir (42 days), followed by glargine products (28 days). Once opened, only vials may be stored in the refrigerator. Expirations for in-use pens are longest for Tresiba® (56 days), followed by Levemir® and Toujeo® (42 days), followed by Lantus® and Basaglar® (28 days).

Table 4: Long-acting, Basal Insulin Storage Requirements[28-32]

Product‡§	Package	Storage		
		Not-in-use *UNOPENED* *Refrigerated*	Not-in-use *UNOPENED* *Room Temp.*	In-use *OPENED*
Insulin glargine				
Lantus®	10 mL vial, 100 units/mL Single vials	Until expiration date	28 days	28 days refrigerated or room temperature
	3 mL SoloStar® PFP (100 units/mL) Package of 5 pens	Until expiration date	28 days	28 days room temperature *DO NOT REFRIGERATE*
Toujeo®	1.5 mL SoloStar® PFP (300 units/mL) Package of 3 or 5 pens	Until expiration date		42-days room temperature *DO NOT REFRIGERATE*

Product‡§	Package	Storage		
Basaglar®	3 mL KwikPen PFP Package of 5 pens	Until expiration date	28 days	28 days room temperature *DO NOT REFRIGERATE*
Insulin detemir				
Levemir®	10 mL vial, 100 units/mL Single vials	Until expiration date	42 days	42-days refrigerated or room temperature
	3 mL FlexTouch® PFP (100 units/mL) Package of 5 pens	Until expiration date	42 days	42-days room temperature *DO NOT REFRIGERATE*
Insulin degludec				
Tresiba®	3 mL FlexTouch® PFP (100 units/mL) Package of 5 pens	Until expiration date	56 days (8 weeks)	56 days room temperature *DO NOT REFRIGERATE*
	3 mL FlexTouch® PFP (200 units/mL) Package of 3 pens	Until expiration date	56 days (8 weeks)	56 days room temperature *DO NOT REFRIGERATE*

Key: ǂKeep products away from direct heat and light; § No basal insulin is approved for mixing with other products, however degludec is manufactured as a 70/30 mixture with insulin aspart (Ryzodeg®) and in combination with liraglutide (Xultophy®).

Utah Medicaid Utilization Data

Utah Medicaid claims data from 2013 to 2016 was used to answer the following questions.

1. What long-acting insulin products are used?

LONG ACTING INSULIN - ALL FFS CLAIMS	2013			2014			2015			2016*			ALL		
PRODUCT	UNITS	CLAIMS	PATIENTS	UNITS	CLAIMS	PATIENTS	UNITS	CLAIMS	PATIENTS	UNITS	CLAIMS	PATIENTS	UNITS	CLAIMS	PATIENTS
TRESIBA FLEX INJ 100UNIT	0	0	0	0	0	0	0	0	0	15	1	1	15	1	1
TRESIBA FLEX INJ 200UNIT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
LEVEMIR INJ	**13,120**	**690**	**163**	**13,460**	**692**	**183**	**12,950**	**685**	**183**	**12,565**	**705**	**163**	**52,095**	**2,772**	**457**
LEVEMIR INJ FLEXPEN	105	7	3	180	12	4	90	6	2	0	0	0	375	25	6
LEVEMIR INJ FLEXTOUC	0	0	0	30	2	1	141	12	7	453	25	5	624	39	12
BASAGLAR INJ 100UNIT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
LANTUS INJ 100/ML	**107,747**	**6,569**	**1,259**	**108,624**	**6,665**	**1,430**	**86,986**	**5,469**	**1,182**	**67,850**	**4,376**	**930**	**371,207**	**23,079**	**2,828**
LANTUS INJ SOLOSTAR	678	53	19	1,332	95	37	1,476	90	32	675	50	19	4,161	288	88
LANTUS FOR INJ OPTICLIK	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TOUJEO SOLO INJ 300IU/ML	0	0	0	0	0	0	197	7	1	435	39	6	632	46	6
TOTAL	**121,650**	**7,319**	**1,417**	**123,626**	**7,466**	**1,624**	**101,840**	**6,269**	**1,367**	**81,993**	**5,196**	**1,097**	**429,109**	**26,250**	**3,252**

LONG ACTING INSULIN - PEDIATRIC FFS CLA	2013			2014			2015			2016*			ALL		
PRODUCT	UNITS	CLAIMS	PATIENTS	UNITS	CLAIMS	PATIENTS	UNITS	CLAIMS	PATIENTS	UNITS	CLAIMS	PATIENTS	UNITS	CLAIMS	PATIENTS
TRESIBA FLEX INJ 100UNIT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TRESIBA FLEX INJ 200UNIT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
LEVEMIR INJ	**100**	**10**	**2**	**160**	**15**	**7**	**210**	**21**	**4**	**60**	**6**	**1**	**530**	**52**	**10**
LEVEMIR INJ FLEXPEN	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
LEVEMIR INJ FLEXTOUC	0	0	0	30	2	1	60	4	1	78	6	1	168	12	2
BASAGLAR INJ 100UNIT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
LANTUS INJ 100/ML	**5,160**	**467**	**101**	**5,780**	**536**	**138**	**5,020**	**457**	**133**	**3,490**	**320**	**87**	**19,450**	**1,780**	**311**
LANTUS INJ SOLOSTAR	165	11	2	120	8	4	150	7	3	105	7	4	540	33	12
LANTUS FOR INJ OPTICLIK	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TOUJEO SOLO INJ 300IU/ML	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL	**5,425**	**488**	**105**	**6,090**	**561**	**146**	**5,440**	**489**	**139**	**3,733**	**339**	**90**	**20,688**	**1,877**	**324**

- The Utah Medicaid Preferred Drug List (PDL) includes Lantus® and Levemir® vials as preferred agents. Use patterns reflect these preferences.
    - Less than 3% of patients received insulin pens versus vials for these products through the end of 2016.
- For both all, and pediatrics, Lantus® use is significantly higher than Levemir®.

- Use of longer-acting/concentrated agents.
    - A single adult patient filled a single claim of 15 mL for Tresiba® (degludec U100) in 2016.
    - A total of six adult patients filled 39 claims for Toujeo® (glargine U300) in 2016.
    - Each of these products is associated with more consistent glycemic control and less hypoglycemia, especially nocturnal.
- Epidemiological evidence (e.g. Centers for Disease Control, CDC) suggests the incidence of diabetes is increasing and guidelines consider the additional of long-acting basal insulin therapy appropriate in most patients. Utah Medicaid claim data suggests that the use of these agents has declined. In 2013, 105 patients had claims submitted for a long-acting insulin, but in 2016 only 90 patients had submitted a claim for long-acting insulin. This may reflect fewer fee-for-service patients with a diagnosis of diabetes, increased use of NPH insulin products for basal insulin coverage or other unknown factors.
    - A review of NPH insulin use, (data not presented) did not demonstrate an increase. Usage of most NPH containing products was consistent from 2013 to 2016, however, use of Novolin NPH had declined by >50% although usage was low (from 68 patients in 2013 to 27 patients in 2016

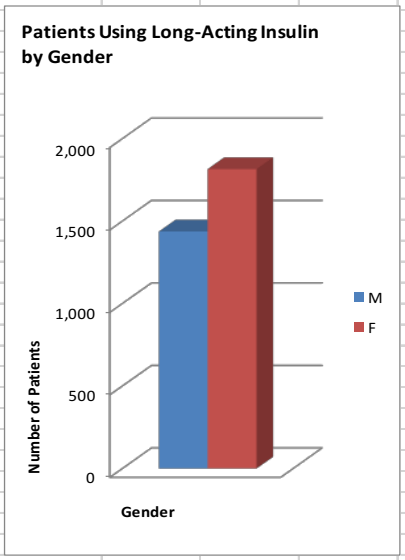
2. Who is being prescribed the long-acting basal insulin products?

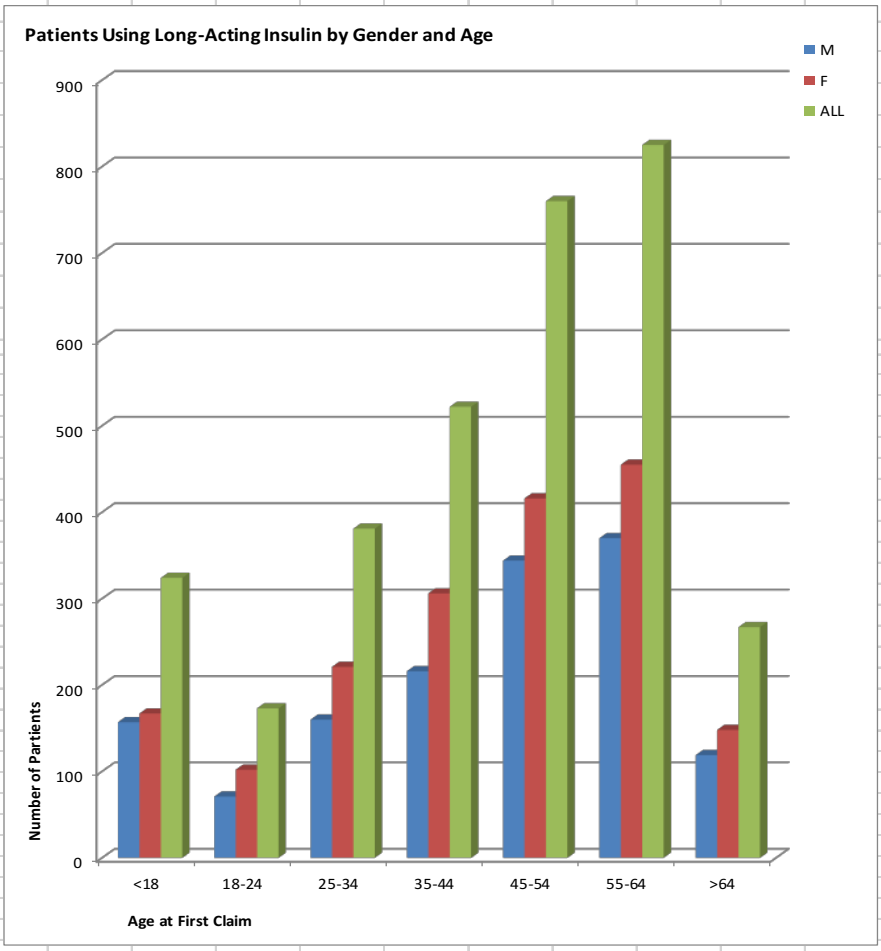
LONG ACTING INSULIN - ALL FFS PATIENTS

TOTAL PATIENTS 2013-2016

AGE*	M	F	ALL
<18	157	167	324
18-24	71	102	173
25-34	160	221	381
35-44	216	306	522
45-54	344	416	760
55-64	370	455	825
>64	119	148	267
TOTAL	1,437	1,815	

* Age at first claim.

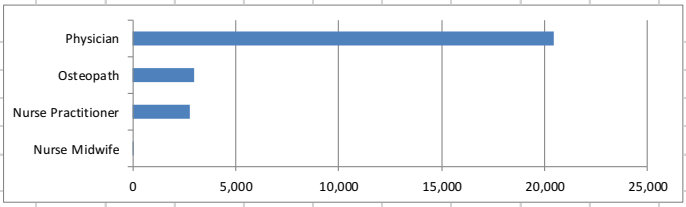




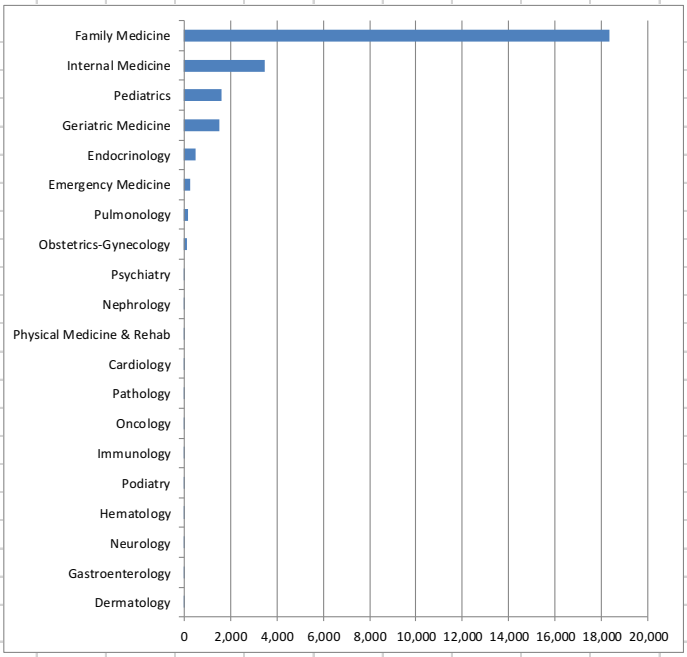
- More women than men use long-acting insulin products.
- At age <18 years, the distribution between males and females is similar. T1DM is more common than T2DM in young people and these results are consistent with epidemiologic evidence suggesting equal gender distribution in T1DM.
- The number of patients using long-acting insulin products drops at age 18, and may reflect the loss of childhood Medicaid benefits for some individuals.
- Use is highest between ages 35 to 64 and likely reflects the adult-onset population with T2DM.

3. Who is prescribing the long-acting insulin products?

LONG ACTING INSULIN - ALL FFS PATIENTS PRESCRIBER TYPE	TOTAL CLAIMS 2013-16	
Nurse Midwife	47	0.18%
Nurse Practitioner	2,757	10.50%
Osteopath	3,008	11.46%
Physician	20,438	77.86%
TOTAL CLAIMS	**26,250**	

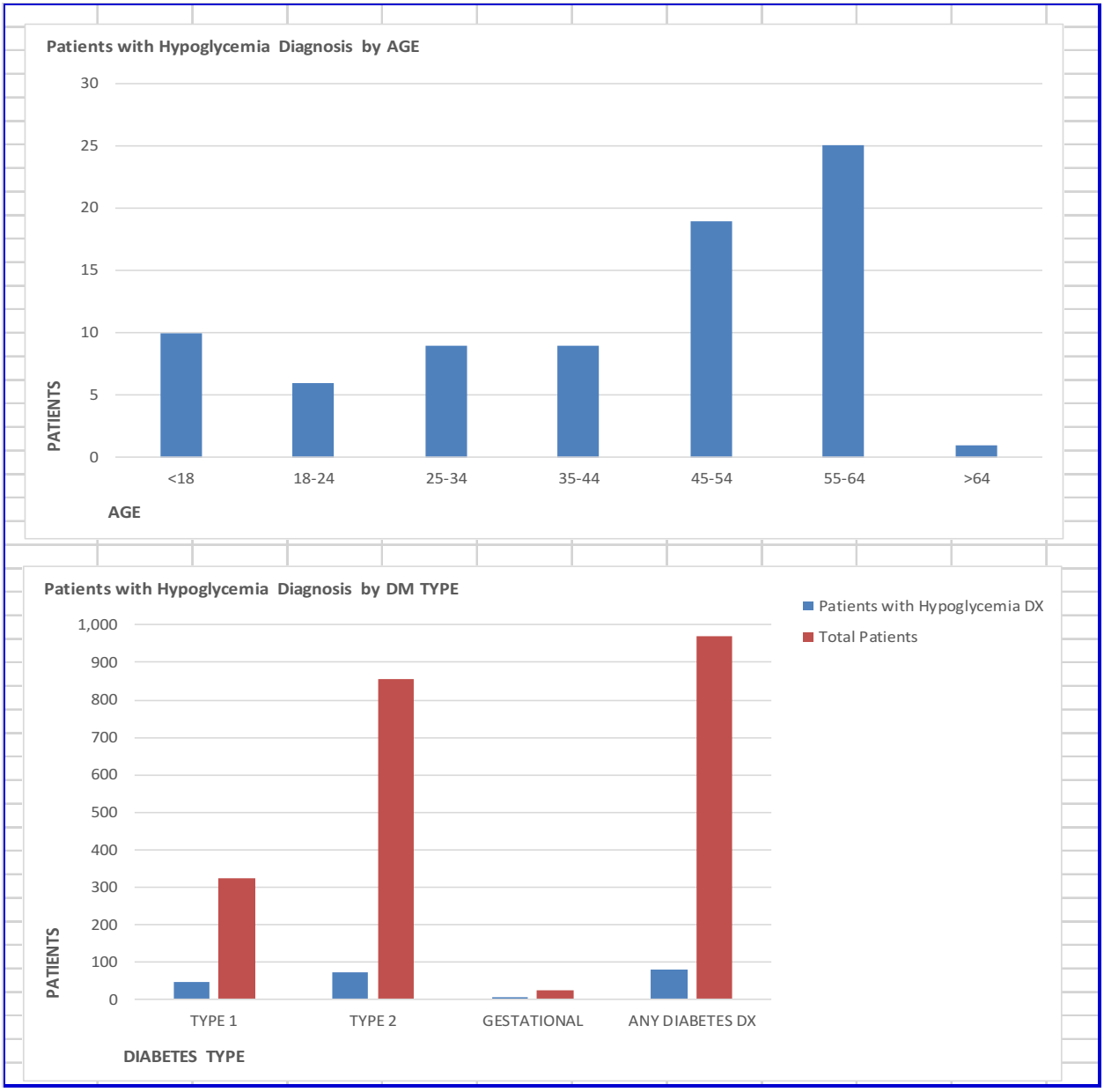


LONG ACTING INSULIN - ALL FFS PATIENTS PRESCRIBER SPECIALTY	TOTAL CLAIMS 2013-16	
Dermatology	1	0.00%
Gastroenterology	1	0.00%
Neurology	1	0.00%
Hematology	2	0.01%
Podiatry	4	0.02%
Immunology	5	0.02%
Oncology	5	0.02%
Pathology	7	0.03%
Cardiology	14	0.05%
Physical Medicine & Rehab	36	0.14%
Nephrology	42	0.16%
Psychiatry	46	0.18%
Obstetrics-Gynecology	143	0.54%
Pulmonology	190	0.72%
Emergency Medicine	262	1.00%
Endocrinology	515	1.96%
Geriatric Medicine	1,514	5.77%
Pediatrics	1,624	6.19%
Internal Medicine	3,487	13.28%
Family Medicine	18,351	69.91%
TOTAL CLAIMS	**26,250**	



- Prescribing specialties match expected prescribing practices.

4. What patients receiving long-acting insulins have experienced at least one documented episode of hypoglycemia?



- Younger patients, likely with T1DM and receiving intensive insulin therapy, have a higher incidence of reported hypoglycemia than young adults.
- The incidence of hypoglycemia reporting increases in older adults but appears to decrease significantly in the elderly. It is unclear if this reflects a true reduction in frequency, reduced reporting, lower intensity of insulin therapy or other factors.
- Overall, Utah Medicaid patients receiving insulin therapy for T1DM, T2DM, gestational diabetes or any diabetes (includes patients with coding for both T1DM and T2DM) have an incidence of reported hypoglycemia similar to epidemiologic evidence (7-15%).

5. Do differences exist in the reporting of at least a single case of hypoglycemia with respect to classification of diabetes or use of any long-acting insulin product?

			2016	DX	DX	DX
GENERIC	**BRAND**	**CLAIMS**	**PATIENTS**	**TYPE 1 DM**	**TYPE 2 DM**	**GEST DM**
Insulin Degludec	Tresiba 100 UNIT/ML	1	**1**	**0**	**1**	**0**
Insulin Detemir	Levemir 100 UNIT/ML	730	**168 (23%)**	**44 (6%)**	**140 (19%)**	**1**
Insulin Glargine	Lantus 100 UNIT/ML	4,426	**944 (21%)**	**284 (6%)**	**731 (17%)**	**21**
Insulin Glargine	Tujeo 300 UNIT/ML	39	**6 (15%)**	**2 (5%)**	**4 (10%)**	**0**
	TOTAL	5,196	**1,097**	**323**	**856**	**22**

AGE	**Patients with Hypoglycemia DX**	**Percent**
<18	10	0.91%
18-24	6	0.55%
25-34	9	0.82%
35-44	9	0.82%
45-54	19	1.73%
55-64	25	2.28%
>64	1	0.09%
TOTAL PATIENTS	**1097**	

TYPE	**Patients with Hypoglycemia DX**	**Total Patients**	**Percent**
TYPE 1	46	323	14.24%
TYPE 2	70	856	8.18%
GESTATIONAL	2	22	9.09%
ANY DIABETES DX	79	971	8.14%

- The incidence of hypoglycemia is similar with Levemir® and Lantus® use for All, T1DM and T2DM patients.
- Fewer patients with gestational diabetes had documented hypoglycemia while receiving Levemir® than Lantus®.
- Hypoglycemia is most common in adults age 45-64.
- Of the 79 patients who developed hypoglycemia while receiving a long-acting insulin in 2016, a larger percentage were diagnosed with T1DM, consistent with a greater likelihood of hypoglycemia in patients prescribed more intensive insulin regimens.

Utilization conclusions: No issues associated with utilization of the long-acting insulins in the Utah Medicaid population were noted.

Conclusion:

Use of insulin in the treatment of diabetes mellitus improves glycemic control, and in T2DM may preserve β-cell function, improve insulin sensitivity and slow disease progression. Guidelines encourage incorporation of insulin into treatment regimens when lifestyle changes and/or oral therapy fail to achieve glycemic targets, or initial A1C levels are high.

The most common complication of insulin therapy is hypoglycemia. The long-acting, basal insulins offer an extended, peakless activity profile with reduced inter- and intrapatient variability. Compared with NPH insulin, the long-acting basal insulins reduce symptomatic and nocturnal hypoglycemia risk. Some guidelines (e.g. American Diabetes Association) suggest that patients at low risk of hypoglycemia may be cost-effectively managed with NPH, while others prefer the pharmacokinetic and pharmacodynamic advantages of the long-acting basal insulins and prefer these first-line (e.g. American Association of Clinical Endocrinologists). Overall, patients requiring basal insulin with a high(er) risk of hypoglycemia or established episodes of hypoglycemia may benefit from the long-acting basal insulin therapy.

A safety review of the long-acting basal insulin products reveals the agents have similar adverse event profiles. The incidence of hypoglycemia is reduced with use of basal insulins compared with NPH. The longer-acting (Tresiba®) and more concentrated product (Toujeo®) may afford even greater ability to reduce hypoglycemia. Cardiovascular safety remains a possible concern with these agents, although the ORIGIN trial supports glargine safety and results from a trial comparing cardiovascular outcomes with degludec and glargine are expected in the near future. Similarly, the risk of cancer with insulin therapy remains ill defined and multiple associations and organizations consider the benefit of insulin therapy to outweigh cancer-risk based on current evidence. Weight gain is associated with insulin therapy and detemir is clearly associated with the lowest weight gain of any basal insulin.

Although the long-acting basal insulins have an improved activity profile, glycemic control is similar to NPH. The advantage of these products is in reduction in hypoglycemia risk, reduction in the number of daily insulin injections, positive effects on weight gain with detemir, and increased dosing flexibility with degludec.

Utah Medicaid Prior Authorization Considerations

Current Quantity Limit:

- Currently the long-acting insulin products are associated with quantity limits. Prescriptions are limited to 60 mL monthly. Ultimately, insulin dosing is individualized.
    - The maximally recommended dosage of long-acting insulins for use in pubescent children and adolescents is 2.0 units/kg/day. The maximally recommended dosage in adults is 1.2 units/kg/day.
        - A quantity of 60 mL U100 long-acting insulin would adequately supply a 100 kg young person (dosed at 2.0 units/kg/day) for 30 days.
        - A quantity of 60 mL U100 long-acting insulin would adequately supply a 167 kg adult dosed at 1.2 units/kg/day for 30 days.

    ❖ *Consider: Prior Authorization override: If an adult weight > 167 kg, or a child > 100 kg, and the physician writes the patient weight on the prescription, no Prior Authorization is required for dispensed quantities > 60 mL/30 days*.

- Should a change be made to reduce quantity limits to the next lowest, commercially available volume (45 mL/month) the impact would be as such;
    - A quantity limit of 45 mL/month would provide a 75 kg young person (2.0 units/kg/day) a 30-day supply
    - A quantity limit of 45 mL/month would provide a 125 kg adult (1.2 units/kg/day) a 30-day supply

Additional Considerations

➢ Consider placing a restriction on insulin pen use in facilities where insulin is administered by staff and not by individual patients.
- This will prevent multiple-patient use of pens and the potential transmission of blood borne pathogens.
- The advantages of pens are established for patient use (*see below*). Professional staff are highly trained, visually and physically unimpaired, and able to manage vial and syringe manipulations

➢ Consider placing no restriction on access to insulin pens for outpatient administration. Insulin pens offer a number of safety advantages
- Insulin administration with pen requires fewer steps than with a vial and syringe
- Pens allow for administration of odd-number dosages. Although rounding doses is not likely a problem with doses above 60 units/day, at lower dosages the difference may be clinically relevant
- Pens are larger, easier to handle, make a click that can be felt and may be preferred for patients with impaired vision or dexterity
    - Exception: patients with arthritis may have more trouble pushing the plunger and patient and prescriber must assess the best mode of insulin administration

- Should a limitation to use of long-acting insulin pens be considered, criteria may include;
  - Clinical diagnosis of T1DM or T2DM with documented labs/tests and prior medication usage (if on prior therapy) in the patient's medical record
  - Must be able to monitor blood glucose
  - Has limitations to syringe/vial insulin administration, including;
    - unable to draw up insulin in a syringe or self-administer, due to mechanical, physical or environmental factors
    - visual impairment
    - requires 1 or more injections during work/school period (this should be uncommon with long-acting insulin use)
  - Lack of capable assistance from a person living with them
  - Has severe phobia to traditional needle/syringe administration (true needle phobia is extremely rare[222])
  - Patient is NOT in an institutional facility
  - *Cognitive impairment (requiring definition)*
  - *History of failure, contraindication or intolerance to preferred agent(s) available in vial(s)*
  - *Clinical rationale supporting a therapeutic advantage*
    - *Compared to vial*
    - *Compared to preferred insulin preparation*

Agent Specific Use Limitations

- Concentrated and Ultra-long Acting Insulins (Toujeo®, insulin glargine 300 units/mL; Tresiba®, degludec U100 and U200)
  - Hypoglycemia risk:
    - Consider the use of concentrated, long-acting insulins (Toujeo or Tresiba U200) in persons at highest risk of hypoglycemia;
      - Patients with multiple prior episodes of hypoglycemia or single episode of severe hypoglycemia
      - Patients with hypoglycemia unawareness
      - Persons unable to detect or self-treat hypoglycemia
      - The elderly with significant renal insufficiency (GFR < 30 mL/min); dosing individualization will be required
      - Presence of preexisting and progressing cognitive deficits that may affect self-care and contribute to administration issues.

- Tresiba® criteria
  - Due to the flexibility in timing of administration, Tresiba may be preferred for people in which there are significant barriers to standardized administration requiring extreme flexibility in dose timing.
    - elderly patients
    - patients with learning difficulties
    - patients who have to rely on health-care professionals for their daily insulin injection

- people whose work/travel/life-style significantly impairs their ability to administer insulin regularly

- Patients requiring > 160 units of insulin per dose and having difficulty with 2-injections per dose of other insulin(s).
  - Tresiba® U200 allows for injection of ≤160 units in a single injection.

➢ Storage/Stability/Waste
- The Preferred Drug List currently includes Levemir® with a long in-use expiration dating. Use of this product, where appropriate, may be particularly useful in poorly adherent patients to minimize waste (particularly if once-daily dosing is possible). Agents with longer expiration dating, once opened, include
  - Tresiba® (56 days), Levemir® (42 days), Toujeo® (42 days)

➢ Authorization Duration: 12 months

---

1. Polonsky W. Patient and provider resistance to initiation and advancing insulin therapy: Improving adherence by evaluating and addressing the emotional and behavioral barriers. Paper presented at: Practical strategies for advancing insulin therapy; November 3, 2016; Grand America Hotal.

References

1. National Diabetes Statistics Report, 2014. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
2. Lexicomp Online. http://online.lexi.com/.
3. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2015;38(1):140-149.
4. Micromedex. Truven Health Analytics, Inc.; 2016. http://www.micromedexsolutions.com/micromedex2/librarian.
5. Thomas SJ, Shin M, McInnis MG, Bostwick JR. Combination therapy with monoamine oxidase inhibitors and other antidepressants or stimulants: strategies for the management of treatment-resistant depression. *Pharmacotherapy.* 2015;35(4):433-449.
6. Mathews M, Gommoll C, Chen D, Nunez R, Khan A. Efficacy and safety of vilazodone 20 and 40 mg in major depressive disorder: a randomized, double-blind, placebo-controlled trial. *International clinical psychopharmacology.* 2015;30(2):67-74.
7. Sbahi HC, B. D. Chronic Constipation: a Review of Current Literature. *Current Gastroenterology Reports.* 2015;17(12).
8. Insulin therapy in type 2 diabetes mellitus. http://www.uptodate.com/contents/insulin-therapy-in-type-2-diabetes-mellitus?source=see_link. Accessed 29 October 2012.
9. Esposito K, Chiodini P, Bellastella G, Maiorino MI, Giugliano D. Proportion of patients at HbA1c target <7% with eight classes of antidiabetic drugs in type 2 diabetes: systematic review of 218 randomized controlled trials with 78 945 patients. *Diabetes, obesity & metabolism.* 2012;14(3):228-233.
10. Basile JN. The potential of sodium glucose cotransporter 2 (SGLT2) inhibitors to reduce cardiovascular risk in patients with type 2 diabetes (T2DM). *J Diabetes Complications.* 2013;27(3):280-286.
11. Mason M, Welsh EJ, Smith I. Drug therapy for obstructive sleep apnoea in adults. *The Cochrane database of systematic reviews.* 2013;5:CD003002.
12. James SP, Mendelson WB. The use of trazodone as a hypnotic: a critical review. *The Journal of clinical psychiatry.* 2004;65(6):752-755.
13. Hadjipavlou G, Mok H, Yatham LN. Pharmacotherapy of bipolar II disorder: a critical review of current evidence. *Bipolar disorders.* 2004;6(1):14-25.
14. 6. Glycemic Targets. *Diabetes Care.* 2017;40(Suppl 1):S48-s56.
15. Standards of medical care in diabetes--2013. *Diabetes Care.* 2013;36 Suppl 1:S11-66.
16. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2012;35(6):1364-1379.
17. Friedman ES, Davis LL, Zisook S, et al. Baseline depression severity as a predictor of single and combination antidepressant treatment outcome: results from the CO-MED trial. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology.* 2012;22(3):183-199.
18. Frye MA, Ketter TA, Leverich GS, et al. The increasing use of polypharmacotherapy for refractory mood disorders: 22 years of study. *The Journal of clinical psychiatry.* 2000;61(1):9-15.
19. Bennett WL, Balfe LM, Faysal JM. AHRQ's comparative effectiveness research on oral medications for type 2 diabetes: a summary of the key findings. *J Manag Care Pharm.* 2012;18(1 Suppl A):1-22.
20. Llorca PM, Lancon C, Brignone M, et al. Relative efficacy and tolerability of vortioxetine versus selected antidepressants by indirect comparisons of similar clinical studies. *Current medical research and opinion.* 2014;30(12):2589-2606.
21. Suppes T, Dennehy EB, Hirschfeld RM, et al. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. *The Journal of clinical psychiatry.* 2005;66(7):870-886.
22. Powers AC. Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine, 19e*. New York, NY: McGraw-Hill Education; 2015.
23. Borgono CA, Zinman B. Insulins: past, present, and future. *Endocrinology and metabolism clinics of North America.* 2012;41(1):1-24.
24. Singh AK, Gangopadhyay KK. Modern basal insulin analogs: An incomplete story. *Indian Journal of Endocrinology and Metabolism.* 2014;18(6):784-793.
25. Owens DR. Clinical evidence for the earlier initiation of insulin therapy in type 2 diabetes. *Diabetes technology & therapeutics.* 2013;15(9):776-785.
26. Papadakis M, McPhee S, Rabow MW, eds. Current Medical Diagnosis and Treatment 2015. 54th ed. New York, NY: McGraw Hill Medical; 2015.
27. Pisano M. Overview of insulin and non-insulin delivery devices in the treatment of diabetes. P T. 2014;39(12):866-876.
28. Tresiba Professional Prescribing Information *Novo Nordisc Inc*. Plainsboro, NJ2017.
29. LLC S-AU. Toujeo Prescribing Information Bridgewater, NJ2015.
30. LLC S-AU. Lantus Prescribing Information Bridgewater, NJ2015.
31. Pharmaceuticals BI. Basaglar Prescribing Information. *Indianapolis, IN*2016.
32. Nordisk N. Levemir Product Information Plainsboro, NJ2015.
33. National Diabetes Education Initiative. http://www.ndei.org.
34. Diabetes Management Guidelines - American Diabetes Association (ADA) 2015 Guidelines. http://www.ndei.org/ADA-diabetes-management-guidelines-pharmacologic-therapy-for-type-1-diabetes.aspx.
35. Claxton AJ CJ, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001;23:1296–1310. doi: 10.1016/S0149-2918(01)80109-0.

36. Yurgin NR, Boye KS, Dilla T, Suriñach NL, Llach XB. Physician and patient management of type 2 diabetes and factors related to glycemic control in Spain. *Patient preference and adherence.* 2008;2:87-95.
37. Ashish K. Jha1, Ronald E. Aubert2, Jianying Yao3, J. Russell Teagarden4 and Robert S. Epstein. Greater Adherence To Diabetes Drugs Is Linked To Less Hospital Use And Could Save Nearly $5 Billion Annually. http://content.healthaffairs.org/content/31/8/1836.full. Accessed 1/11, 2017.
38. Morello CM, Chynoweth M, Kim H, Singh RF, Hirsch JD. Strategies to Improve Medication Adherence Reported by Diabetes Patients and Caregivers: Results of a Taking Control of Your Diabetes Survey. *The Annals of pharmacotherapy.* 2011;45(2):145-153.
39. McGahan L. Afrezza Inhaled Insulin for Diabetes Mellitus [Issues in emerging health technologies issue 120]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2013. http://www.cadth.ca/en/products/environmental-scanning/issues-in-emerging-health-technologies/eh0003-inhaledinsulin. Accessed 13 February 2015.
40. Rajeswari TS. Non invasive insulins: advanced insulin therapy over this decade. Journal of Applied Pharmaceutical Science [Internet]. 2012 [cited 2012 Aug 16];1(8):12-20. http://www.japsonline.com/admin/php/uploads/205_pdf.pdf.
41. Sung SC, Wisniewski SR, Balasubramani GK, et al. Does early-onset chronic or recurrent major depression impact outcomes with antidepressant medications? A CO-MED trial report. *Psychological medicine.* 2013;43(5):945-960.
42. Lamos EM, Younk LM, Davis SN. Concentrated insulins: the new basal insulins. *Therapeutics and Clinical Risk Management.* 2016;12:389-400.
43. Food and Drug Administration. Information on biosimilars. Available at: Http://www.fda.gov/drugs/developmentapprovalapplications/therapeuticbiologicapplications/biosimilars. Accessed 1/11/17.
44. Information on Biosimilars. 2016 https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm.
45. Blevins TC, Dahl D, Rosenstock J, et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus(R)) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. *Diabetes Obes Metab.* 2015;17(8):726-733.
46. Rosenstock J, Hollander P, Bhargava A, et al. Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus(R)) in patients with type 2 diabetes who were insulin-naive or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study). *Diabetes Obes Metab.* 2015;17(8):734-741.
47. Standards of Medical Care in Diabetes - 2017. *Diabetes Care.* 2017;40(Suppl. 1). http://care.diabetesjournals.org/content/40/Supplement_1. Accessed 1/30/17.
48. Committee CPGE. Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. . 2013. http://guidelines.diabetes.ca/fullguidelines.
49. Harper W, Clement M, Goldenberg R, et al. Policies, Guidelines and Consensus Statements: Pharmacologic Management of Type 2 Diabetes-2015 Interim Update. *Can J Diabetes.* 2015;39(4):250-252.
50. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia.* 2012;55(6):1577-1596.
51. Garber AJ, Abrahamson MJ, Barzilay JI, et al. CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM - 2017 EXECUTIVE SUMMARY. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists.* 2017.
52. NICE. Type 1 diabetes in adults: diagnosis and management [NG17]. 2015; https://www.nice.org.uk/guidance/ng17/chapter/introduction. Accessed February 19, 2017.
53. NICE. Type 2 diabetes in adults: management [NG28]. 2015; https://www.nice.org.uk/guidance/ng28/chapter/Introduction. Accessed February 19, 2017.
54. Insulin Pens Must Never Be Used for More than One Person. https://www.cdc.gov/injectionsafety/PDF/Clinical-Reminder-insulin-pen.pdf. Accessed February 15, 2017.
55. Infection Prevention during Blood Glucose Monitoring and Insulin Administration. 2012; https://www.cdc.gov/injectionsafety/blood-glucose-monitoring.html. Accessed February 15, 2017.
56. Draft Guidelines for the Safe Use of Subcutaneous Insulin across the Continuum of Care. 2016; https://www.ismp.org/Tools/guidelines/SUSI/susiguidelines.aspx. Accessed February 16, 2017.
57. Ongoing concern about insulin pen reuse shows hospitals need to consider transitioning away from them. 2013; http://www.ismp.org/Newsletters/acutecare/showarticle.aspx?id=41. Accessed February 15, 2017.
58. NICE. Safer Insulin Prescribing. 2017; https://www.nice.org.uk/advice/ktt20/chapter/options-for-local-implementation. Accessed February 19, 2017.
59. Pharmacologic Management of Type 2 Diabetes: 2016 Interim Update. *Can J Diabetes.* 2016;40(6):484-486.
60. Imran SA, Rabasa-Lhoret R, Ross S. Targets for glycemic control. *Can J Diabetes.* 2013;37 Suppl 1:S31-34.
61. 11. Older Adults. *Diabetes Care.* 2017;40(Suppl 1):S99-s104.
62. 8. Pharmacologic Approaches to Glycemic Treatment. *Diabetes Care.* 2017;40(Suppl 1):S64-s74.
63. 13. Management of Diabetes in Pregnancy. *Diabetes Care.* 2017;40(Suppl 1):S114-s119.
64. 1):S1-S212 CDACPGECCDACPGftPaMoDiCCJDs.
65. 12. Children and Adolescents. *Diabetes Care.* 2017;40(Suppl 1):S105-s113.
66. Rajiv Kovil ea. Consensus on Insulin Dose and Titration Algorithms in Ambulatory Care of Type 2 Diabetes in India. *Journal of The Association of Physicians of India ■ Vol 65 ■ February 2017.*
67. Mannucci E, Giannini S, Dicembrini I. Cardiovascular effects of basal insulins. *Drug, healthcare and patient safety.* 2015;7:113-120.

68. Heise T, Pieber TR. Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogues based on isoglycaemic clamp studies. *Diabetes Obes Metab.* 2007;9(5):648-659.
69. Tibaldi JM. Evolution of insulin: from human to analog. *The American journal of medicine.* 2014;127(10 Suppl):S25-38.
70. Garber AJ. Restaging insulin therapy for patients with type 2 diabetes. *Diabetes Obes Metab.* 2009;11 Suppl 5:1-5.
71. Jehle PM, Micheler C, Jehle DR, Breitig D, Boehm BO. Inadequate suspension of neutral protamine Hagendorn (NPH) insulin in pens. *Lancet.* 1999;354(9190):1604-1607.
72. Kalra S, Unnikrishnan AG, Baruah M, Kalra B. Degludec insulin: A novel basal insulin. *Indian J Endocrinol Metab.* 2011;15(Suppl 1):S12-16.
73. Devries JH, Nattrass M, Pieber TR. Refining basal insulin therapy: what have we learned in the age of analogues? *Diabetes/metabolism research and reviews.* 2007;23(6):441-454.
74. Peterson GE. Intermediate and long-acting insulins: a review of NPH insulin, insulin glargine and insulin detemir. *Current medical research and opinion.* 2006;22(12):2613-2619.
75. Garg SK, Gottlieb PA, Hisatomi ME, et al. Improved glycemic control without an increase in severe hypoglycemic episodes in intensively treated patients with type 1 diabetes receiving morning, evening, or split dose insulin glargine. *Diabetes research and clinical practice.* 2004;66(1):49-56.
76. Robertson KJ, Schoenle E, Gucev Z, Mordhorst L, Gall MA, Ludvigsson J. Insulin detemir compared with NPH insulin in children and adolescents with Type 1 diabetes. *Diabetic medicine : a journal of the British Diabetic Association.* 2007;24(1):27-34.
77. Steinstraesser A, Schmidt R, Bergmann K, Dahmen R, Becker RH. Investigational new insulin glargine 300 U/ml has the same metabolism as insulin glargine 100 U/ml. *Diabetes Obes Metab.* 2014;16(9):873-876.
78. Poon K, King AB. Glargine and detemir: Safety and efficacy profiles of the long-acting basal insulin analogs. *Drug, healthcare and patient safety.* 2010;2:213-223.
79. Pettus J, Santos Cavaiola T, Tamborlane WV, Edelman S. The past, present, and future of basal insulins. *Diabetes/metabolism research and reviews.* 2016;32(6):478-496.
80. Jonassen I, Havelund S, Hoeg-Jensen T, Steensgaard DB, Wahlund P-O, Ribel U. Design of the Novel Protraction Mechanism of Insulin Degludec, an Ultra-long-Acting Basal Insulin. *Pharmaceutical Research.* 2012;29(8):2104-2114.
81. Heise T, Nosek L, Bottcher SG, Hastrup H, Haahr H. Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. *Diabetes Obes Metab.* 2012;14(10):944-950.
82. Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S, Haahr H. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. *Diabetes Obes Metab.* 2012;14(9):859-864.
83. Tresiba Professional Prescribing Information. *Novo Nordisc, Inc*. Plainsboro, NJ2017.
84. Ryzodeg Professional Prescribing Informationa. Bagsvaerd, Denmark: Novo Nordisk A/S; 2015.
85. Heise T, Nosek L, Ronn BB, et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes.* 2004;53(6):1614-1620.
86. Plank J, Bodenlenz M, Sinner F, et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. *Diabetes Care.* 2005;28(5):1107-1112.
87. Becker RHA DR, Bergmann K, Lehmann A, Jax T, Heise T. Diabetes Care. 2015;38(4):637-643.
88. Shiramoto M, Eto T, Irie S, et al. Single-dose new insulin glargine 300 U/ml provides prolonged, stable glycaemic control in Japanese and European people with type 1 diabetes. *Diabetes Obes Metab.* 2015;17(3):254-260.
89. Becker RH, Nowotny I, Teichert L, Bergmann K, Kapitza C. Low within- and between-day variability in exposure to new insulin glargine 300 U/ml. *Diabetes Obes Metab.* 2015;17(3):261-267.
90. Heise T, Hovelmann U, Nosek L, Hermanski L, Bottcher SG, Haahr H. Comparison of the pharmacokinetic and pharmacodynamic profiles of insulin degludec and insulin glargine. *Expert opinion on drug metabolism & toxicology.* 2015;11(8):1193-1201.
91. Lexi-Drugs. Wolters Kluwer; 2015. http://online.lexi.com/lco/action/index/dataset/patch_f. Accessed 11/7/15.
92. Hompesch M, Morrow L, Watkins E, Roepstorff C, Thomsen HF, Haahr H. Pharmacokinetic and pharmacodynamic responses of insulin degludec in African American, white, and Hispanic/Latino patients with type 2 diabetes mellitus. *Clinical therapeutics.* 2014;36(4):507-515.
93. Hompesch M, Troupin B, Heise T, et al. Time-action profile of insulin detemir and NPH insulin in patients with type 2 diabetes from different ethnic groups. *Diabetes Obes Metab.* 2006;8(5):568-573.
94. Sheldon B, Russell-Jones D, Wright J. Insulin analogues: an example of applied medical science. *Diabetes Obes Metab.* 2009;11(1):5-19.
95. Biester T, Blaesig S, Remus K, et al. Insulin degludec's ultra-long pharmacokinetic properties observed in adults are retained in children and adolescents with type 1 diabetes. *Pediatric diabetes.* 2014;15(1):27-33.
96. Danne T, Datz N, Endahl L, et al. Insulin detemir is characterized by a more reproducible pharmacokinetic profile than insulin glargine in children and adolescents with type 1 diabetes: results from a randomized, double-blind, controlled trial. *Pediatric diabetes.* 2008;9(6):554-560.
97. Schober E, Schoenle E, Van Dyk J, Wernicke-Panten K. Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes mellitus. *Journal of pediatric endocrinology & metabolism : JPEM.* 2002;15(4):369-376.
98. DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. 116237, Gestational diabetes mellitus (GDM); [updated 2017 Jan 23, cited 2/24/17]; [about 43 screens]. Available from http://www.dynamed.com/login.aspx?direct=true&site=DynaMed&id=116237. .
99. In: P C, ed. *Hypoglycemia in Diabetes: Pathophysiology, Prevalence, and Prevention*. Alexandria, VA: American Diabetes Association; 2009.
100. Dzygalo K, Golicki D, Kowalska A, Szypowska A. The beneficial effect of insulin degludec on nocturnal hypoglycaemia and insulin dose in type 1 diabetic patients: a systematic review and meta-analysis of randomised trials. *Acta Diabetol.* 2015;52(2):231-238.

101. Heller S, Mathieu C, Kapur R, Wolden ML, Zinman B. A meta-analysis of rate ratios for nocturnal confirmed hypoglycaemia with insulin degludec vs. insulin glargine using different definitions for hypoglycaemia. *Diabetic medicine : a journal of the British Diabetic Association.* 2016;33(4):478-487.
102. Marra LP, Araujo VE, Silva TB, et al. Clinical Effectiveness and Safety of Analog Glargine in Type 1 Diabetes: A Systematic Review and Meta-Analysis. *Diabetes therapy : research, treatment and education of diabetes and related disorders.* 2016;7(2):241-258.
103. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues vs. NPH human insulin in type 1 diabetes. A meta-analysis. *Diabetes Obes Metab.* 2009;11(4):372-378.
104. Sanches AC, Correr CJ, Venson R, et al. Insulin analogues versus human insulin in type 1 diabetes: direct and indirect meta-analyses of efficacy and safety (Provisional abstract). *Brazilian Journal of Pharmaceutical Sciences.* 2013(3):501-509. http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12013070941/frame.html.
105. Sanches AC, Correr CJ, Venson R, Pontarolo R. Revisiting the efficacy of long-acting insulin analogues on adults with type 1 diabetes using mixed-treatment comparisons (Structured abstract). *Diabetes research and clinical practice.* 2011(3):333-339. http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12012011007/frame.html.
106. Szypowska A, Golicki D, Groele L, Pankowska E. Long-acting insulin analogue detemir compared with NPH insulin in type 1 diabetes: a systematic review and meta-analysis. *Polskie Archiwum Medycyny Wewnetrznej.* 2011;121(7-8):237-246.
107. Tricco AC, Ashoor HM, Antony J, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. *BMJ (Clinical research ed).* 2014;349:g5459.
108. Vardi M, Jacobson E, Nini A, Bitterman H. Intermediate acting versus long acting insulin for type 1 diabetes mellitus. *Cochrane Database of Systematic Reviews.* 2008(3).
109. Dailey GE, Gao L, Aurand L, Garg SK. Impact of diabetes duration on hypoglycaemia in patients with type 2 diabetes treated with insulin glargine or NPH insulin. *Diabetes Obes Metab.* 2013;15(12):1085-1092.
110. Owens DR, Traylor L, Mullins P, Landgraf W. Patient-level meta-analysis of efficacy and hypoglycaemia in people with type 2 diabetes initiating insulin glargine 100U/mL or neutral protamine Hagedorn insulin analysed according to concomitant oral antidiabetes therapy. *Diabetes research and clinical practice.* 2017;124:57-65.
111. Rys P, Wojciechowski P, Rogoz-Sitek A, et al. Systematic review and meta-analysis of randomized clinical trials comparing efficacy and safety outcomes of insulin glargine with NPH insulin, premixed insulin preparations or with insulin detemir in type 2 diabetes mellitus. *Acta Diabetol.* 2015;52(4):649-662.
112. Bazzano LA, Lee LJ, Shi L, Reynolds K, Jackson JA, Fonseca V. Safety and efficacy of glargine compared with NPH insulin for the treatment of Type 2 diabetes: a meta-analysis of randomized controlled trials. *Diabetic medicine : a journal of the British Diabetic Association.* 2008;25(8):924-932.
113. Bi Y, Li X, Yang D, et al. Comparative efficacy and safety of long-acting insulin analogs in patients with type 2 diabetes failing on oral therapy: Systemic review and meta-analyses. *Journal of diabetes investigation.* 2012;3(3):283-293.
114. Garber AJ, Clauson P, Pedersen CB, Kolendorf K. Lower risk of hypoglycemia with insulin detemir than with neutral protamine hagedorn insulin in older persons with type 2 diabetes: a pooled analysis of phase III trials. *Journal of the American Geriatrics Society.* 2007;55(11):1735-1740.
115. Freemantle N, Chou E, Frois C, et al. Safety and efficacy of insulin glargine 300 u/mL compared with other basal insulin therapies in patients with type 2 diabetes mellitus: a network meta-analysis. *BMJ Open.* 2016;6(2):e009421.
116. Home PD, Fritsche A, Schinzel S, Massi-Benedetti M. Meta-analysis of individual patient data to assess the risk of hypoglycaemia in people with type 2 diabetes using NPH insulin or insulin glargine. *Diabetes Obes Metab.* 2010;12(9):772-779.
117. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews.* 2007(2).
118. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. *Diabetes research and clinical practice.* 2008;81(2):184-189.
119. Pontiroli AE, Miele L, Morabito A. Increase of body weight during the first year of intensive insulin treatment in type 2 diabetes: systematic review and meta-analysis. *Diabetes Obes Metab.* 2011;13(11):1008-1019.
120. Ritzel R, Roussel R, Bolli GB, et al. Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. *Diabetes Obes Metab.* 2015;17(9):859-867.
121. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care.* 2005;28(4):950-955.
122. Swinnen SG, Simon AC, Holleman F, Hoekstra JB, Devries JH. Insulin detemir versus insulin glargine for type 2 diabetes mellitus. *The Cochrane database of systematic reviews.* 2011(7):Cd006383.
123. Zhuang YG, Peng H, Huang F. A meta-analysis of clinical therapeutic effect of insulin glargine and insulin detemir for patients with type 2 diabetes mellitus. *Eur Rev Med Pharmacol Sci.* 2013;17(19):2566-2570.
124. Einhorn D, Handelsman Y, Bode BW, Endahl LA, Mersebach H, King AB. PATIENTS ACHIEVING GOOD GLYCEMIC CONTROL (HBA1c <7%) EXPERIENCE A LOWER RATE OF HYPOGLYCEMIA WITH INSULIN DEGLUDEC THAN WITH INSULIN GLARGINE: A META-ANALYSIS OF PHASE 3A TRIALS. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists.* 2015;21(8):917-926.
125. Monami M, Mannucci E. Efficacy and safety of degludec insulin: a meta-analysis of randomised trials. *Current medical research and opinion.* 2013;29(4):339-342.
126. Mullins P, Sharplin P, Yki-Jarvinen H, Riddle MC, Haring HU. Negative binomial meta-regression analysis of combined glycosylated hemoglobin and hypoglycemia outcomes across eleven Phase III and IV studies of insulin glargine compared with neutral protamine Hagedorn insulin in type 1 and type 2 diabetes mellitus. *Clinical therapeutics.* 2007;29(8):1607-1619.

127. Ratner RE, Gough SC, Mathieu C, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. *Diabetes Obes Metab.* 2013;15(2):175-184.
128. Russell-Jones D, Danne T, Hermansen K, et al. Weight-sparing effect of insulin detemir: a consequence of central nervous system-mediated reduced energy intake? *Diabetes Obes Metab.* 2015;17(10):919-927.
129. Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2009;180(4):385-397.
130. Vora J, Christensen T, Rana A, Bain SC. Insulin degludec versus insulin glargine in type 1 and type 2 diabetes mellitus: a meta-analysis of endpoints in phase 3a trials. *Diabetes therapy : research, treatment and education of diabetes and related disorders.* 2014;5(2):435-446.
131. Lepercq J, Lin J, Hall GC, et al. Meta-Analysis of Maternal and Neonatal Outcomes Associated with the Use of Insulin Glargine versus NPH Insulin during Pregnancy. *Obstetrics and gynecology international.* 2012;2012:649070.
132. Lv S, Wang J, Xu Y. Safety of insulin analogs during pregnancy: a meta-analysis. *Arch Gynecol Obstet.* 2015;292(4):749-756.
133. Mathiesen ER, Hod M, Ivanisevic M, et al. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. *Diabetes Care.* 2012;35(10):2012-2017.
134. Pollex E, Moretti ME, Koren G, Feig DS. Safety of insulin glargine use in pregnancy: a systematic review and meta-analysis. *The Annals of pharmacotherapy.* 2011;45(1):9-16.
135. Sorli C, Warren M, Oyer D, Mersebach H, Johansen T, Gough SC. Elderly patients with diabetes experience a lower rate of nocturnal hypoglycaemia with insulin degludec than with insulin glargine: a meta-analysis of phase IIIa trials. *Drugs & aging.* 2013;30(12):1009-1018.
136. Freemantle N, Evans M, Christensen T, Wolden ML, Bjorner JB. A comparison of health-related quality of life (health utility) between insulin degludec and insulin glargine: a meta-analysis of phase 3 trials. *Diabetes Obes Metab.* 2013;15(6):564-571.
137. Bronsveld HK, ter Braak B, Karlstad O, et al. Treatment with insulin (analogues) and breast cancer risk in diabetics; a systematic review and meta-analysis of in vitro, animal and human evidence. *Breast cancer research : BCR.* 2015;17:100.
138. Chen YB, Chen Q, Wang Z, Zhou J. Insulin therapy and risk of prostate cancer: a systematic review and meta-analysis of observational studies. *PloS one.* 2013;8(11):e81594.
139. Colmers IN, Bowker SL, Tjosvold LA, Johnson JA. Insulin use and cancer risk in patients with type 2 diabetes: a systematic review and meta-analysis of observational studies. *Diabetes & metabolism.* 2012;38(6):485-506.
140. Dejgaard A, Lynggaard H, Rastam J, Krogsgaard Thomsen M. No evidence of increased risk of malignancies in patients with diabetes treated with insulin detemir: a meta-analysis. *Diabetologia.* 2009;52(12):2507-2512.
141. Du X, Zhang R, Xue Y, et al. Insulin glargine and risk of cancer: a meta-analysis. *The International journal of biological markers.* 2012;27(3):e241-246.
142. Karlstad O, Starup-Linde J, Vestergaard P, et al. Use of insulin and insulin analogs and risk of cancer - systematic review and meta-analysis of observational studies. *Curr Drug Saf.* 2013;8(5):333-348.
143. Tang X, Yang L, He Z, Liu J. Insulin glargine and cancer risk in patients with diabetes: a meta-analysis. *PloS one.* 2012;7(12):e51814.
144. Edwards KL, Riche DM, Stroup JS, et al. Insulin glargine and cancer risk: an opinion statement of the Endocrine and Metabolism Practice and Research Network of the American College of Clinical Pharmacy. *Pharmacotherapy.* 2010;30(9):955-965.
145. Price HI, Agnew MD, Gamble JM. Comparative cardiovascular morbidity and mortality in patients taking different insulin regimens for type 2 diabetes: a systematic review. *BMJ Open.* 2015;5(3):e006341.
146. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *The Cochrane database of systematic reviews.* 2007(2):Cd005613.
147. Sanches ACC, Correr CJ, Venson R, et al. Insulin analogues Versus Human Insulin in Type 1 diabetes: Direct and indirect meta-analyses of efficacy and safety. *Brazilian Journal of Pharmaceutical Sciences.* 2013;49(3):501-509.
148. Wallace JP, Wallace JL, McFarland MS. Comparing dosing of basal insulin analogues detemir and glargine: is it really unit-per-unit and dose-per-dose? *The Annals of pharmacotherapy.* 2014;48(3):361-368.
149. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia.* 2008;51(3):408-416.
150. Swinnen SG, Simon ACR, Holleman F, Hoekstra JB, DeVries JH. Insulin detemir versus insulin glargine for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews.* 2011(7).
151. Swinnen SG, Dain MP, Aronson R, et al. A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. *Diabetes Care.* 2010;33(6):1176-1178.
152. Hollander P, Cooper J, Bregnhoj J, Pedersen CB. A 52-week, multinational, open-label, parallel-group, noninferiority, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes. *Clinical therapeutics.* 2008;30(11):1976-1987.
153. Raskin P, Gylvin T, Weng W, Chaykin L. Comparison of insulin detemir and insulin glargine using a basal-bolus regimen in a randomized, controlled clinical study in patients with type 2 diabetes. *Diabetes/metabolism research and reviews.* 2009;25(6):542-548.
154. Pieber TR, Treichel HC, Hompesch B, et al. Comparison of insulin detemir and insulin glargine in subjects with Type 1 diabetes using intensive insulin therapy. *Diabetic medicine : a journal of the British Diabetic Association.* 2007;24(6):635-642.
155. Marra LP, Araujo VE, Brendon T, et al. Efetividade E Seguranca Da Glargina Vs Detemir E Nph No Tratamento De Pacientes Com Diabetes Tipo 1 - Revisao Sistematica E Metanalise. *Value Health.* 2015;18(7):A862.
156. Product Monograph: Lantus. 2016; http://products.sanofi.ca/en/lantus.pdf. Accessed February 26, 2017.

157. Heller S, Buse J, Fisher M, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet.* 2012;379(9825):1489-1497.
158. Russell-Jones D, Gall MA, Niemeyer M, Diamant M, Del Prato S. Insulin degludec results in lower rates of nocturnal hypoglycaemia and fasting plasma glucose vs. insulin glargine: A meta-analysis of seven clinical trials. *Nutrition, metabolism, and cardiovascular diseases : NMCD.* 2015;25(10):898-905.
159. Freemantle N, Meneghini L, Christensen T, Wolden ML, Jendle J, Ratner R. Insulin degludec improves health-related quality of life (SF-36(R)) compared with insulin glargine in people with Type 2 diabetes starting on basal insulin: a meta-analysis of phase 3a trials. *Diabetic medicine : a journal of the British Diabetic Association.* 2013;30(2):226-232.
160. Hirsch IB, Bode B, Courreges JP, et al. Insulin degludec/insulin aspart administered once daily at any meal, with insulin aspart at other meals versus a standard basal-bolus regimen in patients with type 1 diabetes: a 26-week, phase 3, randomized, open-label, treat-to-target trial. *Diabetes Care.* 2012;35(11):2174-2181.
161. Davies M, Sasaki T, Gross JL, et al. Comparison of insulin degludec with insulin detemir in type 1 diabetes: a 1-year treat-to-target trial. *Diabetes Obes Metab.* 2016;18(1):96-99.
162. Meneghini LF. Intensifying insulin therapy: what options are available to patients with type 2 diabetes? *The American journal of medicine.* 2013;126(9 Suppl 1):S28-37.
163. Home PD, Bergenstal R, Riddle MC, Rojeski M, Espinasse M, Bolli GB. Glycemic control and hypoglycemia with new insulin glargine 300 U/mL in people with type 1 diabetes (EDITION 4). *Diabetes Technology and Therapeutics.* 2015;17:A103-A104.
164. Matsuhisa M, Koyama M, Cheng X, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese adults with type 1 diabetes using basal and mealtime insulin: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 1). *Diabetes Obes Metab.* 2016;18(4):375-383.
165. Bolli GB, Songini M, Trovati M, et al. Lower fasting blood glucose, glucose variability and nocturnal hypoglycaemia with glargine vs NPH basal insulin in subjects with Type 1 diabetes. *Nutrition, metabolism, and cardiovascular diseases : NMCD.* 2009;19(8):571-579.
166. Yki-Jarvinen H, Bergenstal R, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care.* 2014;37(12):3235-3243.
167. Riddle MC, Bolli GB, Ziemen M, Muehlen-Bartmer I, Bizet F, Home PD. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). *Diabetes Care.* 2014;37(10):2755-2762.
168. Matsuhisa M, Koyama M, Cheng X, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese adults with type 1 diabetes using basal and mealtime insulin: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 1). *Diabetes Obes Metab.* 2016;18(4):375-383.
169. Riddle MC, Yki-Jarvinen H, Bolli GB, et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. *Diabetes Obes Metab.* 2015;17(9):835-842.
170. Garber AJ. Treat-to-target trials: uses, interpretation and review of concepts. *Diabetes Obes Metab.* 2014;16(3):193-205.
171. Micromedex® 2.0, (electronic version). Truven Health Analytics; 2015. http://www.micromedexsolutions.com/. Accessed 12/7/15.
172. Powers AC, D'Alessio D. Endocrine Pancreas and Pharmacotherapy of Diabetes Mellitus and Hypoglycemia. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e*. New York, NY: McGraw-Hill Education; 2011.
173. Epocrates. Epocrates, Inc; 2016. Accessed 12/29/16.
174. Clayton D, Woo V, Yale JF. Hypoglycemia. *Can J Diabetes.* 2013;37 Suppl 1:S69-71.
175. Cryer PE, Davis SN. Hypoglycemia. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine, 19e*. New York, NY: McGraw-Hill Education; 2015.
176. Hirsch IB. Insulin analogues. *N Engl J Med.* 2005;352(2):174-183.
177. Freeman JS. Insulin analog therapy: improving the match with physiologic insulin secretion. *The Journal of the American Osteopathic Association.* 2009;109(1):26-36.
178. Swaminathan A. Pharmacology of Insulins. 2015; https://coreem.net/core/pharmacology-of-insulins/ Accessed February 22, 2017.
179. Eriksson JG, Laine MK. Insulin therapy in the elderly with type 2 diabetes. *Minerva Endocrinol.* 2015;40(4):283-295.
180. Meneilly GS, Knip A, Tessier D. Diabetes in the elderly. *Can J Diabetes.* 2013;37 Suppl 1:S184-190.
181. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. *Diabetes Care.* 2000;23(5):639-643.
182. Boyne MS, Saudek CD. Effect of insulin therapy on macrovascular risk factors in type 2 diabetes. *Diabetes Care.* 1999;22 Suppl 3:C45-53.
183. Ritsinger V, Malmberg K, Martensson A, Ryden L, Wedel H, Norhammar A. Intensified insulin-based glycaemic control after myocardial infarction: mortality during 20 year follow-up of the randomised Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI 1) trial. *The lancet Diabetes & endocrinology.* 2014;2(8):627-633.
184. Mellbin LG, Malmberg K, Ryden L, Wedel H, Vestberg D, Lind M. The relationship between glycaemic variability and cardiovascular complications in patients with acute myocardial infarction and type 2 diabetes: a report from the DIGAMI 2 trial. *European heart journal.* 2013;34(5):374-379.
185. Chaitman BR, Hardison RM, Adler D, et al. The Bypass Angioplasty Revascularization Investigation 2 Diabetes randomized trial of different treatment strategies in type 2 diabetes mellitus with stable ischemic heart disease: impact of treatment strategy on cardiac mortality and myocardial infarction. *Circulation.* 2009;120(25):2529-2540.

186. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352(9131):837-853.
187. Gerstein HC, Bosch J, Dagenais GR, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med.* 2012;367(4):319-328.
188. Frier BM, Schernthaner G, Heller SR. Hypoglycemia and cardiovascular risks. *Diabetes Care.* 2011;34 Suppl 2:S132-137.
189. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008;358(24):2545-2559.
190. Monnier L, Colette C, Owens D. Basal insulin analogs: from pathophysiology to therapy. What we see, know, and try to comprehend? *Diabetes & metabolism.* 2013;39(6):468-476.
191. A Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE). 2016; https://clinicaltrials.gov/ct2/show/study/NCT01959529?term=nct01959529&rank=1. Accessed Feb. 7, 2017.
192. Giovannucci E MDTrooarmd-bicotc, prostate, and pancreas. Gastroenterology. 2007; 132:2208-25. .
193. Hsu IR KS, Kabir M et al. Metabolic syndrome, hyperinsulinemia, and cancer. Am J Clin Nutr. 2007; 86:867S-71S. .
194. Smith U GADdtiutrocD-.
195. Vestergaard P, Starup-Linde J. Diabetes, cancer and treatment - a mini-review. *Curr Drug Saf.* 2013;8(5):292-295.
196. Kazda C, Slieker L, Ilag L, Byrd R, Rees T, Prince M. Appraising the mitogenicity of insulin analogues relative to human insulin-response to: Weinstein D, Simon M, Yehezkel E, Laron Z, Werner H. Insulin analogues display IGF-I-like mitogenic and anti-apoptotic activity in cultured cancer cells. Diabetes Metab Res Rev 2009; 25(1): 41-9. *Diabetes/metabolism research and reviews.* 2010;26(3):145-149.
197. Kurtzhals P. Engineering predictability and protraction in a basal insulin analogue: the pharmacology of insulin detemir. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity.* 2004;28 Suppl 2:S23-28.
198. Bolli GB, Hahn AD, Schmidt R, et al. Plasma exposure to insulin glargine and its metabolites M1 and M2 after subcutaneous injection of therapeutic and supratherapeutic doses of glargine in subjects with type 1 diabetes. *Diabetes Care.* 2012;35(12):2626-2630.
199. Nasrallah SN, Reynolds LR. Insulin Degludec, The New Generation Basal Insulin or Just another Basal Insulin? *Clinical medicine insights Endocrinology and diabetes.* 2012;5:31-37.
200. Bordeleau L, Yakubovich N, Dagenais GR, et al. The association of basal insulin glargine and/or n-3 fatty acids with incident cancers in patients with dysglycemia. *Diabetes Care.* 2014;37(5):1360-1366.
201. Muniraj T, Chari ST. Diabetes and pancreatic cancer. *Minerva gastroenterologica e dietologica.* 2012;58(4):331-345.
202. Home PD, Lagarenne P. Combined randomised controlled trial experience of malignancies in studies using insulin glargine. *Diabetologia.* 2009;52(12):2499-2506.
203. Dawson LK, Hamilton LA. Risk of cancer in patients receiving insulin glargine. *Am J Health Syst Pharm.* 2010;67(23):2025-2031.
204. Strandberg AY, Hoti FJ, Strandberg TE, Christopher S, Haukka J, Korhonen P. All-Cause and Cause-Specific Mortality among Users of Basal Insulins NPH, Detemir, and Glargine. *PloS one.* 2016;11(3):e0151910.
205. statement-insulin-glargine-and-cancer ADAAsoigachfdona-.
206. display.cfm?article_id=4932 AAoCE-cArtigcraiD-thmaca.
207. webcast.easd.org/press/glargine/glargine. htm EAftSoDEsLi-saplwcwrfih.
208. The Levemir and Lantus Burn. 2017; http://www.tudiabetes.org/forum/t/the-levemir-and-lantus-burn/10934. Accessed February 25, 2017.
209. Is there a way to make Lantus less painful? https://www.diabetesdaily.com/forum/multiple-daily-injections-mdi/44951-there-way-make-lantus-less-painful/. Accessed February 25, 2017.
210. Karges B, Muche R, Riegger I, et al. Injection of acidic or neutral insulin and pain: a single-center, prospective, controlled, noninterventional study in pediatric patients with type 1 diabetes mellitus. *Clinical therapeutics.* 2006;28(12):2094-2101.
211. Hollander P. Anti-diabetes and anti-obesity medications: Effects on weight in people with diabetes. *Diabetes Spectrum.* 2007;20(3):159-165.
212. Wei W, Pan C, Xie L, Baser O. Real-world insulin treatment persistence among patients with type 2 diabetes. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists.* 2014;20(1):52-61.
213. Abali S, Turan S, Atay Z, Guran T, Haliloglu B, Bereket A. Higher insulin detemir doses are required for the similar glycemic control: comparison of insulin detemir and glargine in children with type 1 diabetes mellitus. *Pediatric diabetes.* 2015;16(5):361-366.
214. Ashwell SG, Gebbie J, Home PD. Twice-daily compared with once-daily insulin glargine in people with Type 1 diabetes using meal-time insulin aspart. *Diabetic medicine : a journal of the British Diabetic Association.* 2006;23(8):879-886.
215. Bryant GA, McDanel DL, Horner KE, Farris KB, Newkirk EN. Evaluation of dosing and clinical outcomes in patients undergoing conversion of insulin glargine to insulin detemir. *Pharmacotherapy.* 2013;33(1):56-62.
216. Nelson SE. Detemir as a once-daily basal insulin in type 2 diabetes. *Clin Pharmacol.* 2011;3:27-37.
217. Le Floch J-P, Lévy M, Mosnier-Pudar H, et al. Comparison of Once- Versus Twice-Daily Administration of Insulin Detemir, Used With Mealtime Insulin Aspart, in Basal-Bolus Therapy for Type 1 Diabetes. *Diabetes Care.* 2008;32(1):32.
218. Insulins (Lexi-Tox). http://online.lexi.com/lco/action/doc/retrieve/docid/lexier/1174339.
219. Kaminer Y, Robbins DR. Insulin misuse: a review of an overlooked psychiatric problem. *Psychosomatics.* 1989;30(1):19-24.
220. Bubb JA, Pontious SL. Weight loss from inappropriate insulin manipulation: an eating disorder variant in an adolescent with insulin-dependent diabetes mellitus. *Diabetes Educ.* 1991;17(1):29-32.
221. A Clinical Reminder About The Safe Use Of Insulin Vials. 2013; https://www.ismp.org/newsletters/acutecare/showarticle.aspx?id=42. Accessed February 27, 2017.

222. Polonsky W. Patient and provider resistance to initiation and advancing insulin therapy: Improving adherence by evaluating and addressing the emotional and behavioral barriers. Paper presented at: Practical strategies for advancing insulin therapy; November 3, 2016; Grand America Hotal.
223. Sanches ACC, Correr CJ, Venson R, Pontarolo R. Revisiting the efficacy of long-acting insulin analogues on adults with type 1 diabetes using mixed-treatment comparisons. *Diabetes research and clinical practice.* 2011;94(3):333-339.

Appendix 1: Long-acting, Basal Insulin Product Comparison[4,28-32,91]

Product	RX	Available Oral Formulations	Labeled Indication	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
Intermediate Acting						
NPH (Human)	**No**	**HumuLIN N (NPH) Kwikpen** Subcutaneous Suspension: 100 U/1 ML **HumuLIN N (NPH)** Subcutaneous Suspension: 100 U/1 ML **NovoLIN N (NPH)** Subcutaneous Suspension: 100 U/1 ML	T1DM T2DM	**T1DM** • SUBQ once or twice daily; individualized **T2DM** • SUBQ: 0.1 to 0.2 units/kg/day once or twice daily ○ with severe hyperglycemia 0.3 to 0.4 units/kg/day SUBQ once or twice daily may be required; may be used in combination with 1 or 2 noninsulin agents (guideline dosing) [2] • maintenance: administer SUBQ once or twice daily; individualize dose to achieve glucose target	**T1DM** • administer SUBQ once or twice daily; individualized dosing **T2DM** • age 10 to 18 years: Individualized dosing	Yes
Long Acting						
Insulin detemir	**Yes**	**Levemir® FlexPen (phasing out)** Subcutaneous Solution: 100 U/1 ML **Levemir® FlexTouch** Subcutaneous Solution: 100 U/1 ML **Levemir®** Subcutaneous Solution: 100 U/1 ML	T1DM T2DM	General Dosage Information • Maximal 80 units per single injection • Unit-to unit conversion for from insulin glargine or NPH insulin • Other insulin therapies may require adjustment of timing and dose of insulin detemir **T1DM** • **Initial:** approximately 1/3 total daily insulin requirement administered SUBQ; use in combination with rapid- or short-acting insulin • **Maintenance**: SUBQ: individualized dose administered once daily with the evening meal or at bedtime OR twice daily in the morning and with the evening meal, at bedtime, or 12 hours after the morning dose; use in combination with rapid- or short-acting insulin **T2DM** **Inadequately controlled on oral antidiabetic agents:** • Initial: 10 units (0.1 to 0.2 units/kg) SUBQ administered once daily in the evening or divided into a twice daily regimen **Inadequately controlled on a glucagon-like peptide-1 (GLP-1) receptor agonist:** • Initial: 10 units SUBQ administered once daily in the evening	Caution: Safety and efficacy not established in children with type 2 diabetes nor in children younger than 2 years with type 1 diabetes **T1DM** **Age ≥2 years** • **Initial**: Approximately 1/3 of total daily insulin dosage SUBQ; use in combination with rapid- or short-acting insulin • **Maintenance**: individualized dosing SUBQ once or twice daily; once daily administration should be with the evening meal or at bedtime; twice daily administration should be in the morning and with the evening meal, at bedtime, or 12 hours after the morning dose; use in combination with rapid- or short-acting insulin	No

Product	RX	Available Oral Formulations	Labeled Indication	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
				• Maintenance: Individualized SUBQ dose administered once or twice daily; once daily administration should be with the evening meal or at bedtime; twice daily administration would be in the morning and with the evening meal, at bedtime, or 12 hours after the morning dose		
Insulin glargine		**Basaglar®** • Subcutaneous Solution: 100 U/1 ML **Lantus® SoloStar** • Subcutaneous Solution: 100 U/1 ML **Lantus®** • Subcutaneous Solution: 100 U/1 ML	T1DM T2DM	General Dosage Information • Maximal 80 units per single injection • Unit-to-unit conversion for Lantus® to Basaglar®. Time of administration should be evaluated • Toujeo® to Lantus®: Initiate at 80% of the Toujeo dose • Once-daily long- or intermediate-acting insulin (eg, NPH insulin) to once-daily Lantus®: Initiate at same dose. A dosage adjustment of the basal insulin may be necessary. Once-daily long- or intermediate-acting insulin (other than another insulin glargine 100 units/mL product) to Basaglar® 100 units/mL: A change in dose may be required. The timing and amount of shorter-acting insulins and doses of other antidiabetic agents may need to be adjusted • Twice-daily NPH insulin to once-daily insulin glargine (Basaglar®, Lantus®) Initiate at 80% of the NPH insulin dose **Type 1 diabetes mellitus** **Basaglar®, Lantus®** • **Insulin-naive:** Initial: approximately 1/3 of total daily insulin requirement administered subQ once daily at the same time every day; adjust dose according to clinical response. Use in combination with short- or rapid-acting, premeal insulin **Type 2 diabetes mellitus** **Basaglar®, Lantus®** • **Insulin-naive**: Initial, up to 10 units (or 0.2 units/kg) subQ once daily at the same time every day. Adjust according to individual metabolic needs, blood glucose measurements, and goals of treatment	General Dosage Information • Unit-to-unit conversion for Lantus® to Basaglar®. Time of administration should be evaluated • Once-daily long- or intermediate-acting insulin (eg, NPH insulin) to once-daily Lantus®: Initiate at same dose; a dosage adjustment of the basal insulin may be necessary. • Once-daily long- or intermediate-acting insulin (other than another insulin glargine 100 units/mL product) to Basaglar® 100 units/mL: A change in dose may be required. The timing and amount of shorter-acting insulins and doses of other antidiabetic agents may require adjustment. • Twice-daily NPH insulin to once-daily Basaglar® or Lantus®: Initiate at 80% of the NPH insulin dose **Type 1 diabetes mellitus** **Basaglar®, Lantus®** • **(6 years or older) Insulin-naive**: Initial, approximately one-third of total daily insulin requirement administered subQ once daily at the same time every day. Adjust dose according to clinical response. Use in combination with short- or rapid-acting, premeal insulin	No (Basaglar a Biosimilar
Ultra-Long Acting						
Insulin glargine U-300 (analog)		**Toujeo®**	T1DM T2DM	**General Dosage Information** • Maximal 80 units per single injection • Lantus® to Toujeo®: Expect that a higher Toujeo® dose will be necessary; Toujeo® dose requirements were 11% to	Not established in pediatrics	No

Product	RX	Available Oral Formulations	Labeled Indication	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
		• Subcutaneous Solution: 300 U/1 ML		17.5% higher than Lantus® requirements in clinical studies • Once-daily long- or intermediate-acting insulin (eg, NPH insulin) to once-daily Toujeo®: Initiate at same dose. A dosage adjustment of the basal insulin may be necessary. • Twice-daily NPH insulin to once-daily Toujeo®: Initiate at 80% of the NPH insulin dose **Type 1 diabetes mellitus** • **Insulin-naive:** Initial: 1/3 to 1/2 of total daily insulin requirement administered subQ once daily at the same time every day; usual dosage, 1 to 80 units per injection; use in combination with short-acting insulin; total daily insulin dose is generally 0.2 to 0.4 units/kg/day; adjust dose no more often than every 3 to 4 days based on blood glucose measurements and goals of therapy; maximum effect may take 5 days **Type 2 diabetes mellitus** • **Insulin-naive**: Initial, 0.2 units/kg subQ once daily; usual dosage, 1 to 80 units per injection; adjust dose no more often than every 3 to 4 days based on blood glucose measurements and goals of therapy; maximum glucose lowering effect may take 5 days		
Insuline degludec (U-100 and U-200)	**Yes**	**Tresiba®** • Subcutaneous Solution: 100 U/1 ML, 200 U/1 ML	T1DM T2DM	**General Dosage Information** • Maximal 80 units per single injection of U100 • Maximal 160 units per single injection of U200 **Type 1 diabetes mellitus** • **Insulin-naive**: Initial dose, 1/3 to 1/2 the total daily insulin dose (general rule for total daily dose, 0.2 to 0.4 units/kg) subQ; remainder of total daily dose given as a short-acting insulin and divided between each daily meal • **Insulin-experienced**: Initiate with same unit dose as the total daily long or intermediate-acting insulin unit dose • **Maintenance dose:** give subQ once daily at any time of the day; titrate to clinical effect with dose increases every 3 to 4 days as needed **Type 2 diabetes mellitus** • **Insulin-naive:,** Initial dose, 10 units subQ once daily	**Type 1 diabetes mellitus** • **(1 year or older) Insulin-naive**: Initial dose, one-third to one-half the total daily insulin dose (general rule for total daily dose, 0.2 to 0.4 units/kg) subQ once daily at the same time each day; remainder of total daily dose given as a short-acting insulin and divided between each daily meal • **(1 year or older) Insulin-experienced**: Initiate at 80% of the total daily long or intermediate-acting insulin unit dose, give subQ once daily at the same time each day • **Dosage titration**: Individualize dose based on patient needs and titrate to clinical effect with dose increases every 3 to 4 days as needed	

Product	RX	Available Oral Formulations	Labeled Indication	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
				• **Insulin-experienced:** Initiate with same unit dose as the total daily long or intermediate-acting insulin unit dose • **Maintenance dose**: give subQ once daily at any time of the day; titrate to clinical effect with dose increases every 3 to 4 days as needed	**Type 2 diabetes mellitus** • **(1 year or older) Insulin-experienced**: Initiate at 80% of the total daily long or intermediate-acting insulin unit dose, give subQ once daily at the same time each day; titrate to clinical effect with dose increases every 3 to 4 days as needed	

Key: FDA=Food & Drug Administration; SubQ=subcutaneous injection

Appendix 2: Evidence

Systematic Reviews and Meta-analysis of Basal Insulins in Type 1 Diabetes

Author #Trials N	Agents	Minimum Trial Duration	Weight Gain kg (↓=less)	HgbA1c %	FPS mg/dL	Insulin Dosage	Any Hypoglycemia	Daytime Hypoglycemia	Nocturnal Hypoglycemia	Severe Hypoglycemia	Adverse Events	Comments
Dzygato K[100] 2015 4 Trials N=1846	degludec vs LAA	12-weeks	N/A	NS	NS	degludec ↓ basal dose Md=-0.042 p=0.0010 degludec ↓ total daily dose Md=-0.07 p=0.002	N/A	N/A	degludec ↓ RR 0.697 p=0.000	N/A	NS	
Heller S[101] 2016 6 Trials N=1910 MA	degludec glargine	26 or 52 weeks	N/A	N/A	N/A	N/A	N/A	N/A	degludec ↓ T1DM NS T2BB (11p-6a) RR 0.73 [0.59, 0.91]	N/A	N/A	N/A
Marra LP[102], 2016 11 trials N=11,246 SR MA	Glargine rDNA insulins (NPH)	>6 months	NS	Adults only glargine ↓ MD -0.26; p=0.02	N/A	NS	N/A	N/A	N/A	glargine ↓ MD=-0.58; p<0.007	N/A	45% Pharma sponsored trial
Monami M[103] 2009 20 trails N=6178 SR MA	LAA NPH	≥12-weeks	detemir ↓ 0.26 kg/m^2 p=0.012	LAA ↓ -0.07%; p=0.026	N/A	N/A	N/A	N/A	LAA ↓ OR=0.69; p<0.01	LAA ↓ OR=0.73; p<0.01	N/A	
Sanches AC[223] 2011 16 trials N=6645 SR MA	Detemir Glargine NPH	4 weeks	N/A	Daily glargine=daily detemir=NPH Twice daily detemir ↓ vs daily glargine -0.14% [0.21 to 0.08]	N/A	N/A	Glargine=NPH Detemir=NPH	N/A	Glargine=NPH Detemir=NPH	N/A	Withdrawal due to AEs detemir 2.9% vs NPH 0.6%; p<0.001 Withdrawals due to lack of efficacy	Analogues offe little to no efficacy advantage over NPH

Author #Trials N	Agents	Minimum Trial Duration	Weight Gain kg (↓=less)	HgbA1c %	FPS mg/dL	Insulin Dosage	Any Hypoglycemia	Daytime Hypoglycemia	Nocturnal Hypoglycemia	Severe Hypoglycemia	Adverse Events	Comments
											detemir 0.4% vs NPH 1.2%; p=0.02 Glargine=detemir	
Sanches AC[147] 2013 35 trials (extracted info for basal insulins) N=4206 SR NMA	Long-acting analogues Short-acting analogues NPH	4 weeks	N/A	Daily glargine=daily detemir Daily glargine or detemir=NPH Twice daily detemir ↓ vs NPH -0.14 p<0.0001	N/A	N/A	Glargine=detemir Detemir=NPH Glargine=NPH	N/A	N/A	N/A	N/A	Few clinical advantages wit long-acting analogues
Szypoweska A[106] 2011 10 trials N=3825 SR MA	detemir NPH	12-weeks	detemir ↓ WMD=-0.779 [-0.992 to -0.567)	detemir ↓ WMD=-0.073 p=0.021	detemir ↓ WMD=-0.977 p<0.001	N/A	N/A	detemir ↓ Rr=0.978 [0.961 to 0.996]	detemir ↓ RR=0.877 [0.816 to 0.942]	detemir ↓ glargine RR=0.665 [0.547 to -0.810]	N/A	
Tricco AC[107] 39 trials N=7496 SR NMA	glargine daily detemir 1-2 x/day NPH 1-2 x daily	N/A	detemir daily vs NPH MD=4.04 [3.06 to 5.02] detemir 1-2x/day vs NPH daily MD=−5.51 [-6.56 to -4.46] glargine daily vs NPH daily MD=-5.14 [-6.07 to -4.21]	glargine daily vs NPH MD=-0.39% [-0.59% to -0.19%] detemir daily vs NPH MD=-0.26% [-0.48% to -0.03%] detemir 1-2x/day vs NPH MD=-0.36% [-0.65% to -0.08%]	N/A	N/A	N/A	N/A	N/A	detemir 1-2x/d ↓ vs NPH 1-2x/day OR=0.62 [0.42 to 0.91]	N/A	Overall, detemi once or twice daily was associated with the least weigh gain; all-cause mortality did n differ between twice daily detemir or NPH No differences incident cancer over 16-26 weeks; QOL wa similar with glargine daily v NPH twice daily

Author #Trials N	Agents	Minimum Trial Duration	Weight Gain kg (↓=less)	HgbA1c %	FPS mg/dL	Insulin Dosage	Any Hypoglycemia	Daytime Hypoglycemia	Nocturnal Hypoglycemia	Severe Hypoglycemia	Adverse Events	Comments
Vardi M[108] 2008 23 trials N=6787 Cochrane Review	LAA NPH	4-weeks	LAA ↓ WMD=-0.67 [-0.87 to -0.45]	LAA ↓ WMD=-0.08 [-0.12 to -0.04]	LAA ↓ WMD=-0.63 [-0.86 to -0.40]	LAA ↓ OR=0.93 [0.8 to 1.08]	NS	N/A	LAA ↓ OR 0.70 [0.63 to 0.79]	LAA ↓ OR=0.73 [0.61 to 0.87]	NS	Modest clinical benefit on nocturnal glucose levels. Effect on overa diabetes contro is clinically unremarkable

Key: [ ]=95% confidence intervals; AE=adverse event; BB=basal/bolus; D=detemir; G=glargine; intermied=intermediate-duration insulin; LAA=long-acting insulin analogues; MA=meta-analysis; MD=mean difference; Md=mean dose; N/A=no evidence presented in study; NPH=neutral protamine Hagedorn insulin; NMA=network meta-analysis; NS=non-statistically significant; OAD=oral antidiabetic drugs; OR=odds ratio; PA=pooled analysis; RR=rate ratio; Rr=relative risk; QOL=quality of life; SR=systematic review; SS=statistically significant;T2BB=type 2 basal bolus; T2IN=type 2 insulin naïve; WMD=weighted mean difference

Systematic Reviews, Pooled Analysis and Meta-analysis of Basal Insulins in Insulin Naïve Type 2 Diabetes

Author #Trials N	Agents	Minimum Trial Duration	Weight Gain Kg (↓=less)	HgbA1c %	FBS mg/dL	Insulin Dosage	Any Hypoglycemia	Daytime Hypoglycemia	Nocturnal Hypoglycemia	Severe Hypoglycemia	Adverse Events	Comments
Dailey GE[109] 2013 4 trials N=2330 PA	Glargine NPH	24-weeks	NPH ↓ Dd <5.8 yr NPH ↓ Dd 9.2-14 yr	Glargine ↓ in higher Dd groups, SS	NSS	NPH ↓ vs glargine in lowest and highest Dd groups, SS		NS	NPH ↑ vs glargine for all Dd; each SS	NPH ↑ vs glargine for Dd >14 years p=0.019	N/A	longer disease wa associated with greater A1C bene longer disease associated with more hypoglycem on NPH
Heller S[101] 2016 6 Trials N=2070 (including extension trials) SR MA	degludec glargine	26 or 52 weeks	N/A	N/A	N/A	N/A	N/A	N/A	Degludec ↓ 12a-6a RR=0.64 [0.48 to 0.86] 10p-6a RR=0.60 [0.45, 0.80]		N/A	
Owens DR 2017 4 trials N=2091 MA	Glargine NPH	24 weeks	NPH ↓ 2.7 vs 2.23 P=0.009	NS	NS	Glargine ↑ 0.42 U/kg vs 0.39 U/kg P=0.03	Glargine ↓ Rr=0.93 P=0.041	N/A	Glargine ↓ Rf=0.73 [0.65 to 0.83] NNH with NPH vs glargine PG<70 mg/dL=12 PG<56 mg/cL=18	NS	N/A	

Author #Trials N	Agents	Minimum Trial Duration	Weight Gain Kg (↓=less)	HgbA1c %	FBS mg/dL	Insulin Dosage	Any Hypoglycemia	Daytime Hypoglycemia	Nocturnal Hypoglycemia	Severe Hypoglycemia	Adverse Events	Comments
Ratner RE[127] 2013 7 trials N=4330 (extracted from trial) MA	degludec vs glargine	26 weeks	N/A	N/A	N/A	N/A	insulin naïve degludec ↓ ERR=0.83 [0.70 to 0.98]	N/A	insulin naïve degludec ↓ ERR=0.64 [0.48 to 0.86]	insulin naïve degludec ↓ ERR 0.14 [0.03 to 0.70]	N/A	Excluded recurrer severe hypoglycemia; reduction in hypoglycemia wa more pronounced maintenance pha

Key: [ ]=95% confidence intervals; AE=adverse event; BB=basal/bolus; D=detemir; Dd=duration of diabetes; G=glargine; intermied=intermediate-duration insulin; LAA=long-acting insulin analogues; MA=meta-analysis MD=mean difference; Md=mean dose; N/A=no evidence presented in study; NPH=neutral protamine Hagedorn insulin; NMA=network meta-analysis; NNH=numbed needed to harm; NS=non-statistically significant; OAD=oral antidiabetic drugs; OR=odds ratio; PA=pooled analysis; RR=rate ratio; Rr=relative risk; QOL=quality of life; SR=systematic review; SS=statistically significant;T2BB=type 2 basal bolus; T2IN=type 2 insulin naïve; WMD=weighted mean difference

Systematic Reviews, Pooled Analysis and Meta-analysis of Basal Insulin with Oral Therapy in Type 2 Diabetes

Author #Trials N	Comparators	Minimum Trial Duration	Weight Gain (↓=less)	HgbA1c %	FBS mg/dL	Insulin Dosage	Any Hypoglycemia	Daytime Hypoglycemia	Nocturnal Hypoglycemia	Severe Hypoglycemia	Adverse Events (AE)	Comments
Rys P[111] 2015 (Extracted from presented data on 28 trials) N=12,669 SR MA	Glargine Detemir NPH (extracted)	12 weeks	With OADs Glargine=NPH Detemir ↓ vs Glargine WMD=0.77 [0.44 to 1.11]	With OADs Glargine=detemir Glargine ↓ vs NPH for A1C goal without hypoglycemia rr=1.32 [1.09 to 1.59] With BB and OAD therapy Glargine=NPH Glargine ↓ vs Detemir rr=1.41 [1.12 to 1.78]	N/A	N/A	Any hypoglycemia Trend favors glargine over NPH rr=0.92 [0.84 to 1.001]		Glargine/OAD ↓ vs NPH/OAD rr=0.63 [0.51 to 0.77]	Glargine/OAD=NPH/OAD	NPH=glargine Withdrawal due to AE Detemir/OAD ↑ vs glargine/OAD rr=0.40 [0.24 to 0.69] Injection site reactions Glargine/OAD ↓ vs detemir/OAD rr=0.22 [0.07 to 0.55]	Treatment satisfaction favored glargine OA vs NPH/OAI WMD=0.60 [0.07 to 1.1 glargine/OA vs detemir/OA P<0.001

Key: [ ]=95% confidence intervals; AE=adverse event; BB=basal/bolus; D=detemir; Dd=duration of diabetes; G=glargine; intermied=intermediate-duration insulin; LAA=long-acting insulin analogues; MA=meta-analysis MD=mean difference; Md=mean dose; MNC=mean net change; N/A=no evidence presented in study; NPH=neutral protamine Hagedorn insulin; NMA=network meta-analysis; NNH=numbed needed to harm; NS=non-statistically significant; OAD=oral antidiabetic drugs; OR=odds ratio; PA=pooled analysis; RR=rate ratio; Rr=relative risk; rr=risk reduction; QOL=quality of life; SR=systematic review; SS=statistically significant;T2BB=type 2 basal bolus; T2IN=type 2 insulin naïve; WMD=weighted mean difference

Systematic Review, Meta-Analysis and Pooled Analysis of Basal Insulin Use in Type 2 Diabetes

Author #trials N	Agents	Minimum Trial Duration	Weight Gain Kg (↓=less)	HgbA1c %	FBS mg/dL	Insulin Dosage	Any Hypoglycemia	Symptomatic Hypoglycemia	Nocturnal Hypoglycemia	Severe	Adverse Events	Comments
Bazzano LA[112] 2008 12 trials N=4385 SR MA	Glargine vs NPH	4-weeks	NPH↓ MNC=-0.33 [-0.61 to -0.06]	NS	NS	similar	glargine↓ p<0.0003	glargine↓ p<0.0001	glargine↓ p<0.0001	NS	NS	
Bi X[113] 2012 22 trials N=9548 (pertinent evidence extracted) SR MA	Long-acting analogues (LAA) NPH	34 weeks (median)	LAA=NPH	LAA=NPH	LAA ↓ vs NPH WMD -0.20 P=0.03	LAA ↓ vs NPH WMD=-0.07 U/kg/day [-0.14 to 0.00] with high heterogeneity	LAA ↓ vs NPH OR 0.57 P<0.00001	N/A	LAA ↓ vs NPH OR=0.46 P<0.0001	NS	No differences in AEs, treatment related AEs or withdrawals	
Garber AJ[114] 2007 3 trials N=1374 Pooled, post-hoc	Insulin detemir vs NPH	22 weeks	detemir ↓ older -1.02 [1.61 to 0.42] younger -1.13 [1.58 to 0.69]	detemir non-inferior to NPH	Similar	similar	detemir ↓ Older Rr=0.59 p=0.002 Younger R=0.75 p=0.02	detemir ↓ in elderly Rr=0.61 [0.42–0.89]	Detemir ↓in younger (p<0.001) but not older group	uncommon	NS	Pooled analysis of phase 3 trials
Freemantle N[115] 2016 41 trials (25 included oral therapy) N=not defined NMA	Glargine U300 vs other insulin therapies	Not defined	U300=detemir U300=degludec	U300=detemir U300=NPH	N/A	U300=detemir U300=NPH U300=degludec	U300=detemir U300=NPH U300=degludec	none significant	U300 ↓ vs NPH RR 0.18 [0.05 to 0.55] U300=detemir U300=degludec	N/A	N/A	Sensitivity analysis suppor robustness
Home PD[116] 2010 5 trials N=3180 MA	Evening glargine vs evening NPH; morning glargine vs evening NPH	24 weeks	N/A	No differences	N/A	No differences	Glargine evening ↓ P<0.001	Glargine morning ↓ p<0.001	Glargine evening ↓ p<0.001 Glargine morning ↓ p<0.001 Severe nocturnal Glargine morning ↓ p<0.001 Glargine evening ↓ P<0.001	NS	N/A	White,european patients; glargine evening NNT=8 a glargine morning NNT=5 t prevent one NPH sympton hypoglycemia

Author #trials N	Agents	Minimum Trial Duration	Weight Gain Kg (↓=less)	HgbA1c %	FBS mg/dL	Insulin Dosage	Any Hypoglycemia	Symptomatic Hypoglycemia	Nocturnal Hypoglycemia	Severe	Adverse Events	Comments
Horvath K[117] 2007 6 trials glargine 2 trials detemir vs NPH each N=2293 on glargine or detemir Cochrane	Glargine and Detemir vs NPH	24 weeks	N/A	NS	similar	N/A	Compared to NPH Glargine NS detemir ↓ Rr=0.82; p<0.0001	Compared to NPH glargine↓ Rr=0.84 p=0.005) detemir ↓ Rr=0.56, p<0.001	Compared to NPH glargine↓ Rr0.66, p<0.0001 detemir ↓ Rr=0.63, p<0.00001	Detemir=NPH Glargine=NPH	Clinically similar	Methodologic quality of t was rated low. "If at all, only a minor clini benefit of treatment with long-acting insulin analogu (LAA) for patients with diabetes mellitus type 2 treated with "basal" insuli regarding symptomatic, nocturnal hypoglycaemic events. Until long-term efficacy and safety data ar available, we suggest a cautious approach to ther with insulin glargine or detemir.
Monami M[118] 2008 14 trials; N=3188 MA	NPH LAA	12 weeks	Detemir ↓ vs NPH detemir ↓ vs glargine p=0.048	NS	NPH=LAA NPH ↓ 0.1% vs detemir	N/A	Detemir=NPH Glargine=NPH	LAA↓ vs NPH OR=0.69 [0.60–0.80]	LAA↓ vs NPH OR=0.46 [0.38–0.55]	similar	N/A	most were sponsored trial different hypoglycemia definitions
Pontiroli AE[119] 2011 46 trials N=14,250 SR MA	Intensive insulin treatment regimens: newer analogues vs older basal vs within prandial vs twice daily	12 weeks	Weight increase was lower with basal regimens vs twice-daily regimens vs prandial regimens	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Body weight increase duri 1st year of insulin treatme depends on insulin regime final A1C, change in A1C, insulin regimen
Ritzel R[120] 2015 3 Trials N=2496 MA	Glargine U300 vs Glargine U100	2 weeks	glargine U300 ↓ p=0.039	similar	similar	Mean Dose 12% higher with U300 U300=0.85 U/kg/day U100=0.76 U/kg/day	glargine U300 ↓SS	U300 ↓SS	U300 ↓ RR=0.69 [0.57–0.84]	U300 ↓ RR=0.86 [0.77–0.97]	No differences	hypoglycemia benefit wit U300 was noted in the init and maintenance period; hypoglycemia rates simila between younger and old persons; NNT to prevent 1 case of severe or confirme hypoglycemia with U300 v 16

Author #trials N	Agents	Minimum Trial Duration	Weight Gain Kg (↓=less)	HgbA1c %	FBS mg/dL	Insulin Dosage	Any Hypoglycemia	Symptomatic Hypoglycemia	Nocturnal Hypoglycemia	Severe	Adverse Events	Comments
Rosenstock J[121] 2005 4 trials N=2304 MA	Glargine NPH	24 weeks	NA	similar	glargine↓ p=0.0344	similar	N/A	glargine ↓ rr=11% p=0.0006	glargine ↓ rr=26% p<0.0001 severe glargine ↓ rr=59% p=0.0231	glargine ↓ rr=46% p=0.0442	N/A	
Swinnen SG[122] 2011 4 trials N=2250 Cochrane	Detemir glargine	12 weeks	detemir ↓ MD=0.91 [-1.21 to -0.61]	similar	glargine ↓ MD=0.34 mmol/L [0.01 to 0.67]	glargine ↓ MD=-0.26 U/kg [0.11 to 0.41]	similar	N/A	similar	similar	detemir ↑ injection site reactions RR=3.31 [1.13 to 9.73]	Detemir dosing was twice daily in 13.6% to 57.2% of subjects; high risk of bias; substantial heterogeneity; clinically relevant differen in efficacy or safety
Zhuang YG[123] 2013 13 trials N=1668 MA	Glargine Detemir	24 weeks	detemir ↓ p<0.00001	similar	similar	detemir ↑ P<0.00001	secondary outcome not well defined; no difference in prevalence	N/A	N/A	N/A	N/A	Detemir is associated wit less weight gain and a hig daily insulin dosage than glargine

Key: [ ]=95% confidence intervals; AE=adverse event; BB=basal/bolus; D=detemir; Dd=duration of diabetes; ERR=estimated rate ratio; G=glargine; intermied=intermediate-duration insulin; LAA=long-acting insulin analogues; MA=meta-analysis; MD=mean difference; Md=mean dose; MNC=mean net change; N/A=no evidence presented in study; NPH=neutral protamine Hagedorn insulin; NMA=network meta-analysis; NNH=numb needed to harm; NS=non-statistically significant; OAD=oral antidiabetic drugs; OR=odds ratio; PA=pooled analysis; RR=rate/risk ratio; Rr=relative risk; rr=risk reduction; QOL=quality of life; SR=systematic review; SS=statistically significant;T2BB=type 2 basal bolus; T2IN=type 2 insulin naïve; WMD=weighted mean difference

Systematic Reviews, Meta-Analysis of Basal Insulin in Combined Assessments of T1DM and T2DM

Author #Trials N	Comparators	Minimum Trial Duration	Weight Gain (↓=less)	HgbA1c %	FBS mg/dL	Insulin Dosage	Any Hypoglycemia	Daytime Hypoglycemia	Nocturnal Hypoglycemia	Severe Hypoglycemia	Adverse Events	Comments
Einhorn D[124] 2015 7 trials N=2044 (extracted from meta-analysis) MA	Degludec vs Glargine*	26 weeks	N/A	Degludec was non-inferior to glargine	N/A	N/A	Maintenance phase Degludec ↓ ERR=0.79 [0.68 to 0.92]	N/A	degludec ↓ ERR=0.63 [0.52 to 0.77]	Severe requiring assistance: degludec ↓ ERR=0.86 [0.76 to 0.98]	N/A	*Study assessed hypoglycemia associated with HgbA1c <7% with Degludec vs Glargi statistically lower hypoglycemia rates wit degludec more pronounced in the maintenance period

Author #Trials N	Comparators	Minimum Trial Duration	Weight Gain (↓=less)	HgbA1c %	FBS mg/dL	Insulin Dosage	Any Hypoglycemia	Daytime Hypoglycemia	Nocturnal Hypoglycemia	Severe Hypoglycemia	Adverse Events	Comments
Monami M[125] 2013 5 trials N=2105 MA	Degludec vs LAA	16 weeks	similar	similar	degludec ↓ SS	degludec ↑ SS in T2DM	degludec ↓ SS in T2DM	N/A	degludec ↓ SS in T1DM	N/A	Fewer with degludec	Basal with oral or prandial insulin
Mullins P[126] 2007 11 trials N=5074 MRA	Glargine vs NPH	not stated	N/A	N/A	N/A	N/A	glargine ↓ T1DM and T2DM P<0.05 sustained when adjusted for end-point A1C	N/A	glargine↓ in T1DM, p<0.05 symptomatic glargine ↓ in T1DM/T2DM p<0.05	glargine ↓SS in T1DM glargine ↓ in T1DM/T2DM p<0.05	N/A	Negative binomial meta-regression; sponsored trials; hypoglycemia rates increased at lower HgbA1c values; severe hypoglycemia rates reduced 16%-46.8% with glargine; low overall rates of hypoglycemia
Ratner RE[127] 2013 7 trials N=4330 MA	degludec vs glargine	26 weeks	N/A	N/A	N/A	N/A	T2DM degludec ↓ ERR 0.83 [0.74 to 0.94]	N/A	T2DM degludec ↓ ERR 0.68 [0.57 to0.82] T1DM degludec↓ during maintenance ERR 0.75 [0.60 to 0.94]	T2DM degludec ↓ SS	N/A	Excluded recurrent, severe hypoglycemia reduction in hypoglycemia was more pronounced in maintenance phase
Russell-Jones D[158] 2015 7 trials N=4317 MA	degludec vs glargine	26 weeks	N/A	degludec non-inferior to glargine	degludec ↓ T2DM p<0.05 T1DM p<0.05 T1DM degludec ↓ for titration period p<0.05 for end of trial p<0.05	N/A	N/A	N/A	T1DM maintenance period Degludec ↓ RR=0.74 [0.60 to 0.94] T2DM Degludec ↓ End of trial RR 0.68 [0.57 to 0.82] Maintenance period RR=0.62 [0.49 to 0.78] T1DM and T2DM Degludec ↓ End of trial RR=0.75 [0.65 to 0.85] Titration period RR=0.86 [0.74 to 1.00] Maintenance period RR=0.68 [0.58 to 0.80]	N/A	N/A	nocturnal confirmed hypoglycemia was lower with degludec T2DM SS Pooled T1&T2DM SS

Author #Trials N	Comparators	Minimum Trial Duration	Weight Gain (↓=less)	HgbA1c %	FBS mg/dL	Insulin Dosage	Any Hypoglycemia	Daytime Hypoglycemia	Nocturnal Hypoglycemia	Severe Hypoglycemia	Adverse Events	Comments
Singh SR[129] 2009 49 trials N>6000 MA	Glargine detemir NPH	not stated	similar	T1DM glargine ↓ vs NPH WMD=-0.11 [-0.21 to -0.02] Detemir=NPH Detemir=glargine T2DM Glargine ↓ vs NPH without OAD WMD=0.28 [0.07 to 0.49] Detemir ↓ vs NPH With OAD WMD=0.13 [0.03 to 0.22] Detemir-BB ↓ vs glargine-BB WMD=0.20 [0.10 to 0.30]	N/A	N/A	Detemir-BB ↓ vs NPH-BB RR=0.66 [0.45 to 0.96]	N/A	T1DM Adults detemir↓ vs NPH RR=0.92 [0.85-0.98] Children & Adolescents detemir↓ vs NPH RR=0.85 [0.77 to 0.94] T2DM Adults Glargine ↓ vs NPH with OAD RR=0.56 [0.47 to 0.68] Glargine ↓ vs NPH without OAD RR=0.78 [0.62 to 0.98] Detemir ↓ vs NPH with OAD RR=0.53 [0.31 to 0.91]	T1DM Detemir ↓ vs NPH RR=0.74 [0.58 to 0.96] T2DM Glargine=NPH with or without OAD Detemir=NPH with OAD	Similar, serious events were uncommon	evidence suggests little benefit vs conventional insulins for glycemic control reduced hypoglycemia
Vora J[130] 2014 7 trials N=4740 MA	Degludec vs glargine	26 weeks	N/A	degludec non-inferior to glargine in T1DM-BB or T2DM or T2DM insulin naïve	degludec ↓ T1DM-BB MD=-0.61 [-1.13 to -0.10] T2DM insulin-naïve MD=-0.34 [-0.54 to -0.15]	degludec ↓ T1DM-BB ETR=0.88 [0.85 to 0.92] T2DM insulin-naïve ETR=0.90 [0.85 to 0.96]		Degludec ↓ T2DM-BB ERR=0.83 [0.69 to 0.99]	degludec ↓ T1DM-BB ERR=0.83 [0.69 to 0.99] T2DM-BB ERR=0.75 [0.57 to 0.98] T2DM insulin-naïve ERR=0.64 [0.47 to 0.86]	N/A	N/A	

Key: [ ]=95% confidence intervals; AE=adverse event; BB=basal/bolus; D=detemir; Dd=duration of diabetes; ERR=estimated rate ratio; ETR=estimated treatment ratio; G=glargine; intermied=intermediate-duration insuli LAA=long-acting insulin analogues; MA=meta-analysis; MD=mean difference; Md=mean dose; MNC=mean net change; MRA=meta-regression analysis; N/A=no evidence presented in study; NPH=neutral protamine Hagedorn insulin; NMA=network meta-analysis; NNH=numbed needed to harm; NS=non-statistically significant; OAD=oral antidiabetic drugs; OR=odds ratio; PA=pooled analysis; RR=rate/risk ratio; Rr=relative risk; rr=risk reduction; QOL=quality of life; SR=systematic review; SS=statistically significant;T2BB=type 2 basal bolus; T2IN=type 2 insulin naïve; WMD=weighted mean difference

Systematic Review, Meta-analysis, Randomized, Controlled Trials for Special Populations

Study details	Author Trials N	Comparison Group	Glycemic Efficacy	Maternal Outcomes	Fetal Outcomes	Hypoglycemia	Comment
Gestational, pregestational diabetes	Lepercq J[131] 8 trials N=702	Glargine NPH	No differences	Maternal outcomes NS	No differences	No differences	No significant efficacy or safety-relate outcome issues
Diabetes in pregnancy	Lv S[132] 8 glargine trials N=708 2 detemir trials N=326 (extracted data)	Glargine detemir NPH	N/A	Glargine=NPH; Detemir=NPH	Glargine=NPH; Detemir=NPH	Glargine=NPH; Detemir=NPH	Safe treatment options in pregnancy without maternal or fetal complicatio
Glycemic control and maternal hypoglycemia	Mathiesen ER[133] N=310 Single RCT	Detemir-BB vs NPH-BB	A1C target Detemir-BB noninferior to NPH-BB FPG Detemir-BB ↓ vs NPH-BB @24 GWs, p=0.012 @36 GWs, p=0.017	Serious adverse events were more common in the detemir group (40 vs 31%, NS) similar deterioration of retinopathy similar weight gain and insulin doses	N/A	No differences between all/diurnal/nocturnal major and minor hypoglycemia	
Fetal safety in pregestational and gestational diabetes	Pollex E[134] 8 trials N=702	Glargine NPH	N/A	N/A	No differences	N/A	Data from cohort studies may not be reliable
Elderly Age 65+ T1DM & T2DM	Sorli C[135] 7 trials N=917	degludec vs glargine	N/A			Proportion of patients with confirmed hypoglycemia was similar between treatment groups T1DM 97.7% degludec, 94.1% glargine T2DM 58.7% both degludec and glargine T2DM Overall confirmed hypoglycemia over treatment period ERR=0.76 [0.61 to 0.95] Nocturnal confirmed hypoglycemia ERR 0.64 [0.43 to 0.95] T1DM	Excluded hypoglycemic unawareness, episode of severe hypoglycemia, serio comorbidity All trials funded by Pharma

Study details	Author Trials N	Comparison Group	Glycemic Efficacy	Maternal Outcomes	Fetal Outcomes	Hypoglycemia	Comment
						Nocturnal confirmed hypoglycemia Degludec (69.8%) ↓ vs glargine (82.4%) ERR=0.76 [0.61 to 0.95] T2DM Nocturnal confirmed hypoglycemia in Degludec ↓ (21.2%) vs glargine (25.4%) ERR=0.64 [0.43 to 0.95] Nocturnal hypoglycemia for maintenance period Degludec=glargine	
Elderly Hypoglycemia risk T2DM	Garber AJ[114] 3 trials N=1374	detemir vs NPH	A1C detemir non-inferior FBS similar			Al hypoglycemic episodes detemir ↓ Rr=0.59 [-0.42 to -0.83] symptomatic hypoglycemia detemir ↓ Rr=0.61 [0.42 to 0.89] Nocturnal episode Rr similar severe episodes uncommon	Weight Mean treatment difference, detemir -1.02 kg [1.61 to 0.42] Mean insulin dosage similar

Key: ERR=estimated rate ratio; N/A=no evidence presented in study; GWs=gestation weeks; NPH=neutral protamine Hagedorn insulin; NS=non-statistically significant; Rr=relative risk; SS=statistically significant; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus

Systematic Review and Meta-Analysis Comparing Long-Acting Basal Insulins Effects on Quality of Life

Trial Type	Author #trials N	Comparators	Minimum Trial Duration	Glycemic Control	FBS	Overall Hypoglycemia	Nocturnal Hypoglycemia	Health Status Improvement (Overall)	Health Status Improvement (Mental)
Health-related QOL (health utility)	Freemantle N[136] 2013 6 trials N=4001	Insulin degludec vs insulin glargine	26 weeks	Degludec non-inferior	No difference	degludec ↓ NS	degludec ↓ SS	degludec ↑ modest but SS	N/A
Health-related QOL (SF-36)	Freemantle N[159] 2013 3 trials N=1922	Insulin degludec vs insulin glargine, each with oral anti-diabetic drugs in insulin naïve	26 weeks	A1C degludec non-inferior	Degludec ↓ (2/3 trials SS, trend favoring in 1 trial)	degludec ↓ SS	degludec ↓ SS	degludec ↑ SS	degludec ↑ SS

Key: A1C=hemoglobin A1c; NS=non-statistically significant; QOL=quality of life; SF-36=health-related quality of life 36-item Short Form; SS=statistically significant

Systematic Reviews, Meta-Analysis, Expert Opinion on Cancer Risk and Basal Analogue Insulin Use

Author Trials N	Insulin type	Cancer type	Cancer incidence increased	Cancer incidence decreased	Cancer incidence unchanged	Comments
Bronsveld HK[137] 16 in vitro; 5 animal; 2 in vivo human; 29 epidemiologic Number not given	glargine vs non-glargine	Breast	glargine ↑ In vivo breast cancer cell lines (epidemiologic studies do not show an increased risk)			No compelling evidence that any insulin analogue is assocaited with increased breast cancer risk; studies underpowered, methodological limitations

Author Trials N	Insulin type	Cancer type	Cancer incidence increased	Cancer incidence decreased	Cancer incidence unchanged	Comments
Chen YB[138] 11 trials N=205,528 males N=7053 prostate cancer cases	insulin vs other glucose-lowering agents glargine vs non-glargine	Prostate			Insulin vs other glucose-lowering agents glargine vs other insulin	There was no substantial evidence for an increased risk of prostate cancer with insulin glargine vs non-glargine insulin use
Colmers IN[139] 19 trials N=1,332,120 With N=41,947 cancers	Insulins glargine	Various	Pancreatic ↑ (new insulin or new glargine use) Prostate ↑ with glargine	Colorectal ↓ with glargine		Pancreatic cancer risk increased with insulin use, perhaps due to reverse causality.
Dejgaard A[140] 16 trials; N=6644 (detemir vs NPH) 5 trials; N=2049 (detemir vs glargine)	detemir glargine NPH	Various	NPH ↑ any cancer risk vs detemir glargine ↑ vs detemir, NS		detemir vs glargine	Company sponsored(All Novo Nordisk-sponsored RCT in T1DM or T2DM)
Du X[141] 7-cohort studies Number not provided	glargine vs non-glargine	Various			Overall and for breast, prostate, pancreatic and gastrointesinal cancers	Open-label studies; evidence does not support an increased cancer risk in persons treated with glargine
Karlstad O[142] 42 trials Number not provided	glargine vs non-glargine	Various	Glargine ↑ breast	Glargine ↓ colon		methodological limitations and confounders
Tang X[143] 11 trials N=448,028 (N=19,128 with cancer)	glargine vs non-glargine	Various		Glargine ↓ vs non-glargine	Breast, prostate pancreas, respiratory tract	RCT and observational studies; low quality evidence
Edwards KL[144] Opinion Statement of the Endocrine and Metabolism Practice and Research Networ of the American College of Clinical Pharmacy	glargine	Various	tenuous relationship			should not affect choice of initial insulin therapy pending additional information

Key: NS=non-statistically significant; RCT=randomized, controlled trials; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus

Systematic Review of Cardiovascular Morbidity and Mortality Associated With Different Insulin Regimens in Type 2 Diabetes

Author #trials N	Outcomes	Results
Price H[145] 2015 8 Trials N=109,910	Primary outcomes: cardiovascular morbidity and mortality includuing fatal and/or non-fatal myocardial infarction, fatal and/or non-fatal stroke, major adverse cardiac events and cardiovascular death. Secondary outcome: All-cause mortality	"Quantitative synthesis of the results from included studies was not possible due to a large amount of clinical heterogeneity. Each study evaluated cardiovascular outcomes across different insulin-exposure contrasts. RCTs did not identify any difference in cardiovascular risks among a fixed versus variable insulin regimen, or a prandial versus basal regimen, albeit clinically important risk and benefits cannot be ruled out due to wide CIs. Findings from cohort studies were variable with an increased and decreased risk of cardiovascular events and all-cause mortality being reported."

Key: OAD=oral antidiabetic drugs; G=glargine; D=detemir; N/A=no evidence presented in study; SS=statistically significant; NS=non-statistically significant; BB=basal/bolus